

Schulten HJ, Hussein D, Al-Adwani F, Karim S, Al-Maghrabi J, Al-Sharif M, Jamal A, Bakhashab S, Weaver J, Al-Ghamdi F, Baeesa SS, Bangash M, Chaudhary A, Al-Qahtani M.

[Microarray expression profiling identifies genes, including cytokines, and biofunctions, as diapedesis, associated with a brain metastasis from a papillary thyroid carcinoma.](#)

*American Journal of Cancer Research* 2016, 6(10), 2140-2161.

**Copyright:**

AJCR Copyright © 2016. Published under the “Creative Commons Attribution Noncommercial License”, enabling the unrestricted non-commercial use, distribution, and reproduction of the published article in any medium, provided that the original work is properly cited.

**Journal website:**

<http://www.ajcr.us/index.html>

**Link to published article:**

<http://www.ajcr.us/files/ajcr0033540.pdf>

**Date deposited:**

17/01/2017



This work is licensed under a [Creative Commons Attribution-NonCommercial 3.0 Unported License](https://creativecommons.org/licenses/by-nc/3.0/)

## Original Article

# Microarray expression profiling identifies genes, including cytokines, and biofunctions, as diapedesis, associated with a brain metastasis from a papillary thyroid carcinoma

Hans-Juergen Schulten<sup>1,2</sup>, Deema Hussein<sup>3</sup>, Fatima Al-Adwani<sup>1,4</sup>, Sajjad Karim<sup>1,2</sup>, Jaudah Al-Maghrabi<sup>5,6</sup>, Mona Al-Sharif<sup>4</sup>, Awatif Jamal<sup>5</sup>, Sherin Bakhshab<sup>1,7</sup>, Jolanta Weaver<sup>7</sup>, Fahad Al-Ghamdi<sup>5</sup>, Saleh S Baeesa<sup>8</sup>, Mohammed Bangash<sup>8</sup>, Adeel Chaudhary<sup>1,2</sup>, Mohammed Al-Qahtani<sup>1,2</sup>

<sup>1</sup>Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia; <sup>2</sup>KACST Technology Innovation Center in Personalized Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; <sup>3</sup>King Fahad Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; <sup>4</sup>Department of Biology, King Abdulaziz University, Jeddah, Saudi Arabia; <sup>5</sup>Department of Pathology, Faculty of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia; <sup>6</sup>Department of Pathology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia; <sup>7</sup>Institute of Cellular Medicine, Newcastle University, Newcastle NE2 4HH, United Kingdom; <sup>8</sup>Division of Neurosurgery, Department of Surgery, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Received September 21, 2016; Accepted September 23, 2016; Epub October 1, 2016; Published October 15, 2016

**Abstract:** Brain metastatic papillary thyroid carcinomas (PTCs) are afflicted with unfavorable prognosis; however, the underlying molecular genetics of these rare metastases are virtually unknown. In this study, we compared whole transcript microarray expression profiles of a *BRAF* mutant, brain metastasis from a PTC, including its technical replicate (TR), with eight non-brain metastatic PTCs and eight primary brain tumors. The top 95 probe sets (false discovery rate (FDR)  $p$ -value < 0.05 and fold change (FC) > 2) that were differentially expressed between the brain metastatic PTC, including the TR, and both, non-brain metastatic PTCs and primary brain tumors were in the vast majority upregulated and comprise, e.g. *ROS1*, *MYBPH*, *SLC18A3*, *HP*, *SAA2-SAA4*, *CP*, *CCL20*, *GFAP*, *RNU1-120P*, *DMBT1*, *XDH*, *CXCL1*, *PI3*, and *NAPSA*. Cytokines were represented by 10 members in the top 95 probe sets. Pathway and network analysis ( $p$ -value < 0.05 and FC > 2) identified granulocytes adhesion and diapedesis as top canonical pathway. Most significant upstream regulators were lipopolysaccharide, TNF, NKkB (complex), IL1A, and CSF2. Top networks categorized under diseases & functions were entitled migration of cells, cell movement, cell survival, apoptosis, and proliferation of cells. Probe sets that were significantly shared between the brain metastatic PTC, the TR, and primary brain tumors include *CASP1*, *CASP4*, *C1R*, *CC2D2B*, *RNY1P16*, *WDR72*, *LRRC2*, *ZHX2*, *CITED1*, and the noncoding transcript AK128523. Taken together, this study identified a set of candidate genes and biofunctions implicated in, so far nearly uncharacterized, molecular processes of a brain metastasis from a PTC.

**Keywords:** Papillary thyroid carcinoma, brain metastasis, microarray expression profiling, cytokines, diapedesis

## Introduction

Approximately 80% of all thyroid carcinomas are histologically classified as papillary thyroid carcinomas (PTCs). PTCs harbor in 40-70% of the cases a *BRAF* V600E mutation that renders *BRAF* in a constitutively active formation and has shown to confer vulnerability to protease inhibitors [1]. In thyroid cancer, the V600E mutation is frequently associated with unfavor-

able features including multifocality, lymph node involvement, and distant metastasis. We reported earlier on the comparison between V600E positive and negative PTCs and normal thyroid samples, revealing that V600E positive PTCs are comparably afflicted with more unfavorable features; however, both V600E positive and negative PTCs exhibited quite closely related expression profiles when compared to normal thyroid samples [2].

Common sites of distant PTC metastases are lung and bone whereas metastases to the brain are rare. Frequency of brain metastases varies between 0.15-1.3% of all diagnosed thyroid carcinomas [3]. Brain metastases can occur even after years of the primary thyroid tumor with an approximately 10 years difference of patients' mean age; however, aggressive subtypes of PTC as tall cell variants are likely to metastasize earlier than other histological subtypes [4]. Prognosis for patients with intracranial brain metastasis of a PTC is in general poor and depends on factors like histology type and the presence of other distant metastases [5]. In approximately 10% of patients who die from thyroid carcinoma reveal to have a brain metastasis at autopsy [6].

Symptoms implicative for a brain metastasis include headache, nausea, seizure, polyuria, and various neuronal impairments such as ocular motor vision dysfunction. Asymptomatic brain metastases from thyroid cancer are very rare and can be incidentally detected by  $^{131}\text{I}$  treatment. Treatment options include surgery, radiation, and systemic therapy. Surgical resection of a brain metastasis originating from differentiated thyroid cancer may improve prognosis of patients [6]. Sorafenib which is a dual-active inhibitor that inhibits the mitogen activated protein kinase pathway has been successfully applied to treat a patient with a brain metastasis originating from a follicular thyroid carcinoma [7]. It is proposed that the brain metastatic process is a multistep process involving migration, intravasation, circulation, arrest, extravasation, and settlement/invasion of the brain microenvironment [8, 9].

In the present study, using whole transcript microarrays, we analyzed the expression profile of a brain metastasis from a PTC and compared it with those from non-brain metastatic, stage III and IV PTCs and with primary brain tumors. Our objectives were to identify molecular biomarkers that are specifically related to the brain metastatic PTC and that support unraveling molecular mechanisms underlying this deteriorative disease.

### Material and methods

#### *Tumor samples*

In the core expression analysis we studied samples from one brain metastatic PTC, eight non-

brain metastatic, stage III and IV PTCs and eight primary brain tumors. The specimens were derived from patients who were treated surgically in the period between 2010 and 2015 at the King Abdulaziz University Hospital, Jeddah, and the King Faisal Specialist Hospital and Research Center (KFSH&RC), Jeddah. Histopathological diagnosis was performed by a team of pathologists (JM, AJ, and FG) on established criteria. The brain metastasis was initially identified as a left frontal brain tumor in a middle-aged (< 45 years) old female without any known chronic illness and the tumor was treated by surgery. Histopathological examination sustained the diagnosis of a metastatic PTC and subsequent sonography demonstrated thyroid nodules and the primary, stage II [10], multifocal PTC and lymph node metastases were resected. This study was approved by the Research Ethics Committee of the King Abdulaziz University, Faculty of Medicine, #358-10, #976-12, and the Institutional Review Board of the KFSH&RC, #IRB2010-07.

#### *Immunohistochemistry*

Antibodies (Ventana Medical Systems, Tucson, AZ) employed for immunohistochemistry (IHC) consisted of thyroid transcription factor (TTF-1) (clone 8G7G3/1), thyroglobulin (clone 2H11/6E1), and proliferation marker ki-67 (clone 30-9) which is immunoreactive in the late G1, S, G2, and M phases of the cell cycle. Four  $\mu\text{m}$  sections of formalin-fixed and paraffin-embedded specimens were processed on an automated immunostainer (BenchMark XT, Ventana Medical Systems) according to the manufacturer's protocols and using the ultraView Universal DAB Detection Kit for detection.

#### *RNA and microarray processing*

Isolation of total RNA and microarray sample processing were performed as described earlier [14, 15]. In brief, the Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA) was employed to assess RNA integrity and integrity number was > 5 in samples used for the differential expression analysis between then brain metastatic PTC, non-brain metastatic PTCs, and primary brain tumors. The NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE) was utilized to determine RNA concentration. All RNA samples were processed using the Ambion WT Expression Kit (Life Technologies, Austin, TX), the GeneChip

WT Terminal Labeling and Controls Kit (Affymetrix, Santa Clara, CA), and the Affymetrix GeneChip Hybridization, Wash and Stain Kit. The RNA from the brain metastasis was processed twice to generate a technical replicate (TR). All processed samples were hybridized to Affymetrix Human Gene 1.0 ST GeneChip arrays. This type of microarray interrogates with a set of 764,885 probes 36,079 annotated reference sequences (NCBI build 36). The microarrays were scanned on a GeneChip Scanner 3000 7G and probe cell intensity data (CEL) files were generated using the GeneChip Command Console Software (AGCC).

## *Sample selection for microarray expression study*

Sample selection criterion was to identify probe sets which are significant to the brain metastatic process. Therefore, eight non-brain metastatic, stage III and IV PTCs as advanced thyroid tumors and eight selected primary brain tumors were chosen for differential expression analysis. For selection, analysis of variance (ANOVA) in Partek Genomics Suite version 6.6 (Partek Inc., MO) was employed and performed on the imported CEL files and carried out between the comparison group, consisting of the brain metastatic PTC and its TR, and each of 40 primary brain tumors for which CEL files were available from our microarray data sets. Eight primary brain tumors with meningioma histology revealed to have the comparably lowest numbers of differentially expressed probe sets with the brain metastatic PTC and its TR ( $p$ -value  $< 0.05$  and  $FC > 2$ ) and therefore were taken, after assessing sample bias, as a group for differential gene expression analysis which included also, besides the brain metastatic PTC and its TR, the eight non-brain metastatic PTC group. Sample bias was assessed by replacing the eight primary brain tumors with comparably lowest numbers of differentially expressed probe sets with those eight brain tumors having the highest number of differentially expressed probe sets. The ANOVA result of the assessment showed that approximately 90% of the significantly differentially expressed probe sets were shared between both configurations.

## *Gene expression core analysis*

In Partek Genomics Suite quality assessment of microarray experiments was performed on

basis of QC metrics tables and QC graphical reports on the imported CEL files. The saved distribution file of 18 quantile normalized samples was used for quantile normalization of subsets of the 18 CEL files, i.e. 17 CEL files consisting of eight non-brain metastatic PTCs, eight primary brain tumors and either the brain metastatic PTC or its TR. All lists of differentially expressed probe sets were generated by applying ANOVA and using either a  $p$ -value  $< 0.05$  and a fold change (FC)  $> 2$  or using, where indicated, the more stringent criterion of the false discovery rate (FDR)  $p$ -value (step-up method)  $< 0.05$ , and fold change (FC)  $> 2$ . Principal component analysis was employed to illustrate overall variance in gene expression between samples or groups of samples. Average linkage hierarchical clustering was performed by using Spearman's correlation as a similarity matrix. Venn diagrams were generated to display intersecting or non-intersecting groups of differentially expressed probe sets. The Gene Ontology (GO) enrichment tool was employed in the gene expression workflow to group significantly expressed genes into functional categories. The gene enrichment score utilizes the Fisher's Exact test to determine the level of differential gene expression in a functional category. PANTHER version 10 which combines GO annotations and a phylogenetic tree model for inferring gene functions was primarily used for protein classification [16]. The generated microarray data set has been deposited at the NCBI Gene Expression Omnibus under accession number GSE66463 and it includes renormalized samples from non-brain metastatic PTCs and primary brain tumors of submissions GSE54958 [2, 17] and GSE77259 [11].

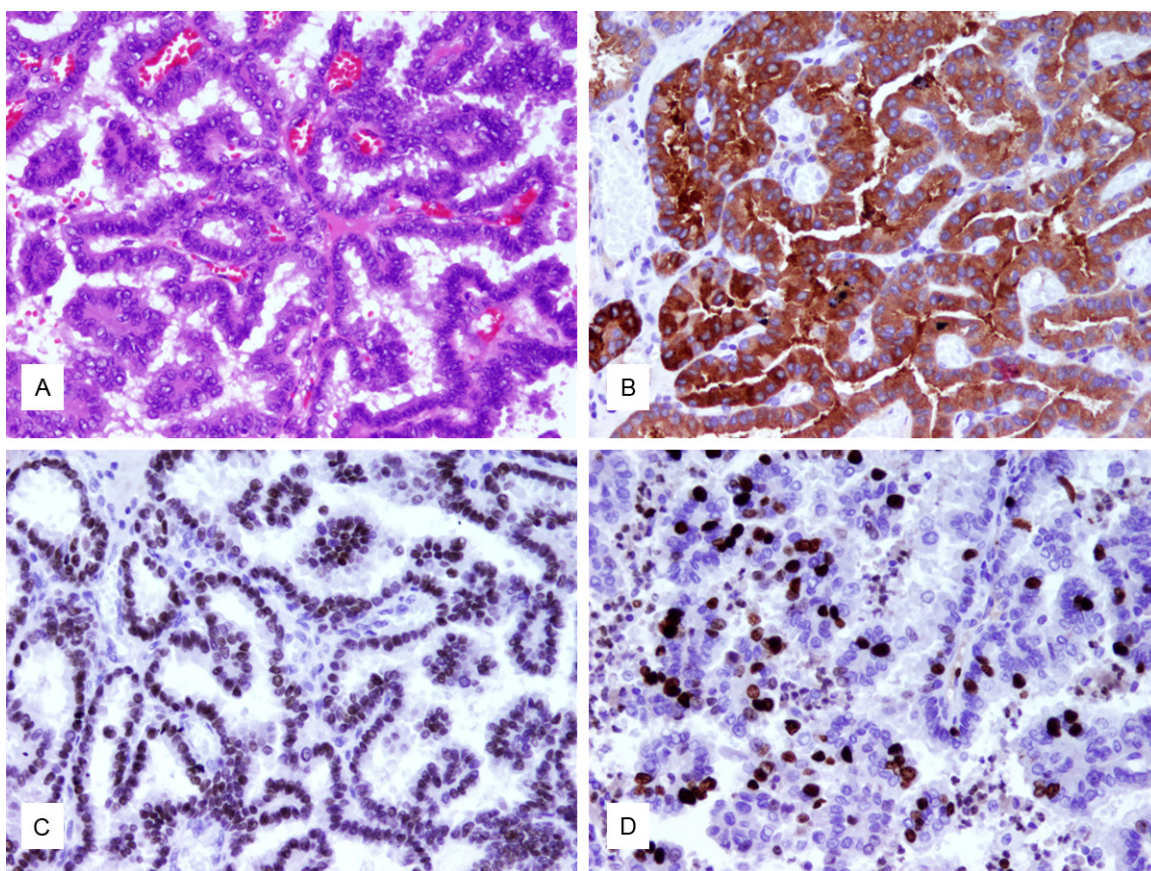
## *Functional network and pathway analysis*

The Ingenuity Pathways Analysis software (IPA; build version 338830M) (Ingenuity Systems, Redwood City, CA) was utilized to interpret biological significance of expression data [18]. IPA workflow comprises core and functional analysis and structural data categorization. The Ingenuity Knowledge Base was used as a reference data set. Direct and indirect molecular relationships were included in the analysis settings. Fisher's exact test  $p$ -values indicate the significance of relationships between the analyzed data set molecules and the functional frameworks prebuilt or generated *de novo* by IPA. Where specified, the Molecule Activity



**Table 1.** Primer sequences used for semiquantitative RT-PCR

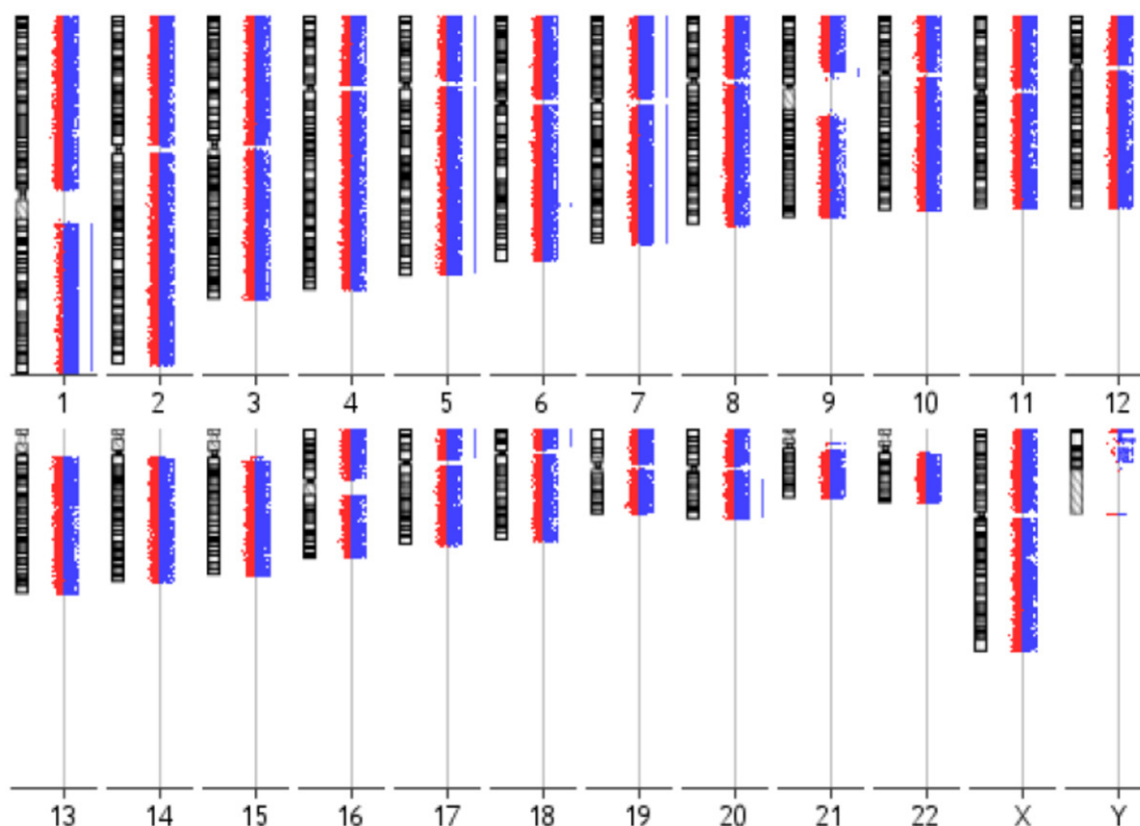
| Gene           | Forward primer sequence (5'-3') | Reverse primer sequence (5'-3') | Product size (bp) |
|----------------|---------------------------------|---------------------------------|-------------------|
| <i>ROS1</i>    | ATTGTGGAGAGTTGCACG              | ATGACCTTGCCATCTGTG              | 205               |
| <i>MYBPH</i>   | CCAGTCCAGCAATGATGG              | AGGCTTAGTGGCTGTGGA              | 202               |
| <i>SLC18A3</i> | GCGAAGACGTGAAGATCG              | ATGGCTATGCCAGACGTG              | 240               |
| <i>HP</i>      | CTACACCCTAACTACTCC              | ACATACTTCAGATGGTCAGT            | 184               |
| <i>CP</i>      | ACCCTGATAACACCACAG              | AAGGTCCGATGAGTCCTG              | 185               |
| <i>CCL20</i>   | ACCATGTGCTGTACCAAG              | ATGTCACAGCCTTCATTGG             | 178               |
| <i>GFAP</i>    | GCTTTGCCAGCTACATCG              | ATTGTCCTCTCAACCTC               | 193               |
| <i>SAA2</i>    | TTTTCGTTCTTGCGAG                | CTCTCTACAGTTCAGCTG              | 192               |



**Figure 1.** The brain metastatic PTC. A. Hematoxylin-eosin staining reveals papillary architectures covered by cuboidal to columnar epithelium. Cellular crowding is visible and neoplastic cells demonstrate nuclear clearing and nuclear grooves. B. TTF-1 staining as a marker for thyroid or lung origin exhibits strong nuclear staining. C. Thyroglobulin shows strong cytoplasmic staining. D. Proliferation marker Ki67 is positive in 20% of cells (original magnification, x400).

Predictor was utilized to predict expression effects/coherence of expression effects of a molecule on other pathway or network molecules. The canonical pathway workflow was employed to identify molecules from the uploaded data set that are co-expressed in a directional, up- to downstream, pathway. The overlap percentage of uploaded molecules

matching to a canonical pathway determines its overrepresentation and ranking. Upstream regulators analysis was employed to explain how differences in target gene expression are regulated by upstream molecules and what kind of biological activities are involved. The activation z-score predicts the activation states of regulators. The diseases & functions net-



**Figure 2.** aCGH karyogram of the brain metastatic PTC. Each chromosome ideogram is shown with the green/red fluorescent profiles representing oligonucleotide features. Bars to the right of the profiles indicate gains affecting chromosomes/chromosomal regions including 1q, 5, 7, 12p12pter, 17p, 18p, and 20q.

work analysis was employed to explore relationships and effects between the uploaded data set and downstream processes. The activation z-score measures in how far downstream processes are either up- or downregulated.

#### *Semiquantitative RT-PCR and BRAF mutational analysis*

Expression of eight genes was assessed by semiquantitative RT-PCR using housekeeping gene *B2M* as reference. Primer sequences of the genes are listed in **Table 1** and in case of *B2M* have been reported previously [11]. RT-PCR were performed in 20  $\mu$ L volumes containing each 2  $\mu$ L buffer mix, 0.1% 2-mercapto-ethanol, 0.0125% BSA, 3 mM  $MgCl_2$ , 10 nmol of each dNTP, 5 pmol forward primers, 5 pmol reverse primers, 1.25 units GoTaq DNA Polymerase (Promega, Madison, WI), and 200 ng of second strand cDNA template that was generated using the Ambion WT Expression Kit. No cDNA template was included in the negative control. A modified standard PCR protocol was

used as reported earlier [11]. Gel band densities of selected reactions were measured using ImageJ 1.49v [12] and then the ratio to the internal reference *B2M* was calculated. DNA extraction and *BRAF* mutational screening for the non-brain metastatic PTCs was reported earlier (GSE54958) and for the brain metastatic PTC was performed within the present study as described by us [13].

#### *aCGH analysis*

aCGH study of the brain metastatic PTC was performed according to the manufacturer's protocol (Agilent Technologies, Santa Clara, CA). In brief, tumor DNA was extracted by using the QIAmp DNA FFPE tissue kit (Qiagen, Hilden, Germany). Subsequently, 500 ng of tumor DNA and 500 ng fragmented Agilent, gender-matched reference DNA were labeled using ULS-Cy3 and ULS-Cy5 reagents (Genomic DNA ULS labeling kit), respectively. The hybridization mixture, containing 5  $\mu$ g human Cot-1 DNA, 1  $\mu$ L 100x blocking reagent, 2x Hi-RPM hybridization

**Table 2.** Demographic data and clinicopathological tumor features

| Case       | Histology <sup>1</sup>                  | Age | Gender <sup>2</sup> | Tumor location <sup>3</sup>              | Tumor stage |
|------------|---|-----|---------------------|--|-------------|
| TM-1039-11 | Conventional PTC                        | 52  | F                   | Jugular vein wall                        | IV          |
| TM-989-11  | FVPTC                                   | 71  | F                   | Skull, bone                              | IV          |
| TM-602-11  | Conventional PTC                        | 59  | F                   | Thyroid bed, lung                        | IV          |
| TM-187-11  | Conventional PTC                        | 56  | M                   | Lymph node, perithyroidal extension      | IV          |
| TM-892-11  | Conventional PTC                        | 56  | M                   | Thyroid bed                              | IV          |
| TM-279-08  | Conventional PTC                        | 77  | M                   | Cervical and retropharyngeal lymph nodes | III         |
| TM-301-12  | FVPTC                                   | 51  | F                   | No recurrence/metastasis                 | III         |
| TM-824-12  | Conventional PTC                        | 55  | F                   | Extrathyroidal extension                 | IV          |
| Jed51_MTT  | Conventional PTC                        | 44  | F                   | Brain, left frontal                      | II          |
| Jed04_MN   | Transitional meningioma                 | 57  | F                   | Left tentorial                           | I           |
| Jed13_MN   | Meningothelial meningioma               | 50  | F                   | Left frontal                             | I           |
| Jed49_MN   | Atypical meningioma with brain invasion | 51  | F                   | Posterior right subfalcaline             | II          |
| Jed57_MN   | Transitional meningioma                 | 48  | F                   | Left parasagittal                        | I           |
| Jed64_MN   | Fibroblastic meningioma                 | 49  | F                   | Right frontal                            | I           |
| Jed70_MN   | Fibroblastic meningioma                 | 73  | F                   | Right temporal                           | I           |
| Jed88_MN   | Secretory meningioma                    | 43  | M                   | Sub-occipital                            | I           |
| Jed92_MN   | Meningothelial meningioma               | 49  | F                   | Olfactory groove                         | I           |

<sup>1</sup>FVPTC, follicular variant of PTC; <sup>2</sup>F, female, M, male; <sup>3</sup>Tumor location, location of PTC recurrence/metastasis and location of primary brain tumors including one recurrence (Jed49\_MN).

buffer, and both labeled DNA solutions was hybridized for 40 hrs at 65°C and 20 rpm to a 180K SurePrint G3 Human CGH microarray. The type of microarray contains 170,334 distinct biological features. Subsequently, the microarray was washed stringently, then scanned using the SureScan High resolution scanner, and the generated TIFF image analyzed, utilizing CytoGenomics v3.0.6 software (Agilent Technologies) according to its user guide (G1662-90046). Confidence of differential expression of biological features is based on *p*-values that are generated using the log ratios of the Cy3 to Cy5 channel signals and the log ratio errors which are a measure for the significance of computed log ratios.

## Results

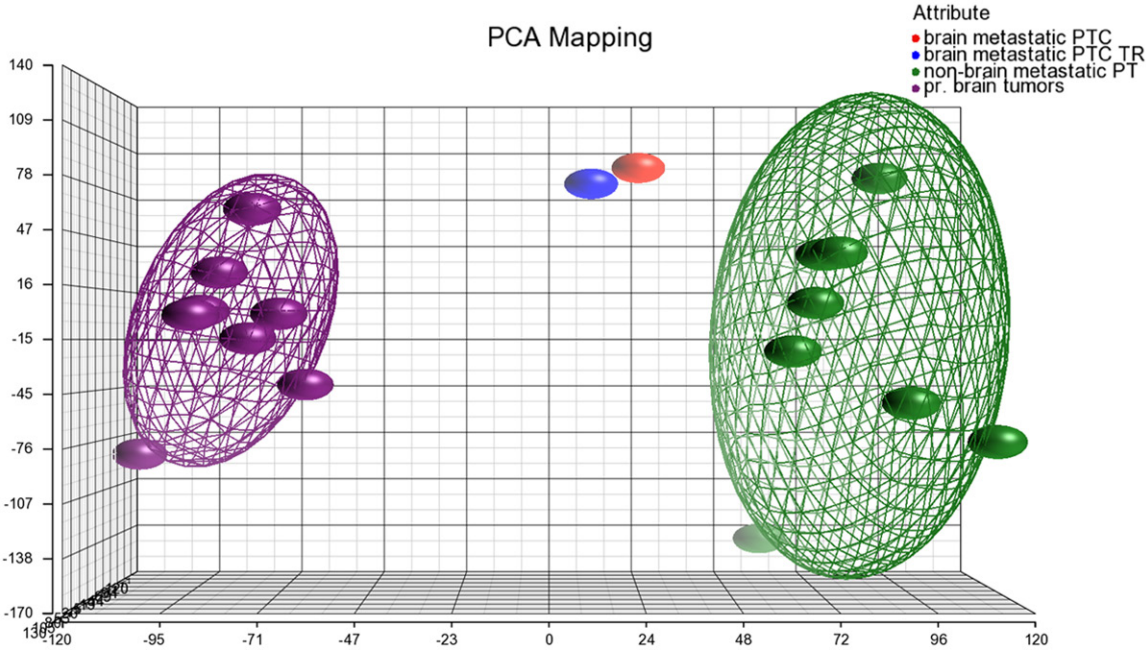
Hematoxylin-eosin staining revealed a characteristic papillary architecture of the brain metastatic PTC (**Figure 1A**). Nuclear immunoreactivity for TTF-1 and cytoplasmic immunoreactivity for thyroglobulin demonstrated origin of the brain metastasis from a PTC (**Figure 1B, 1C**). Proliferation marker Ki-67 showed immunoreactivity in about 20% of the tumor cells (**Figure 1D**). Five of the non-brain metastatic PTCs and the brain metastatic PTC exhibited a *BRAF* V600E mutation. An aCGH analysis of the brain

metastasis identified a number of whole and partial chromosomal gains including +1q, +5, +7, +12p12pter, +17p, +18p, and +20q (**Figure 2**).

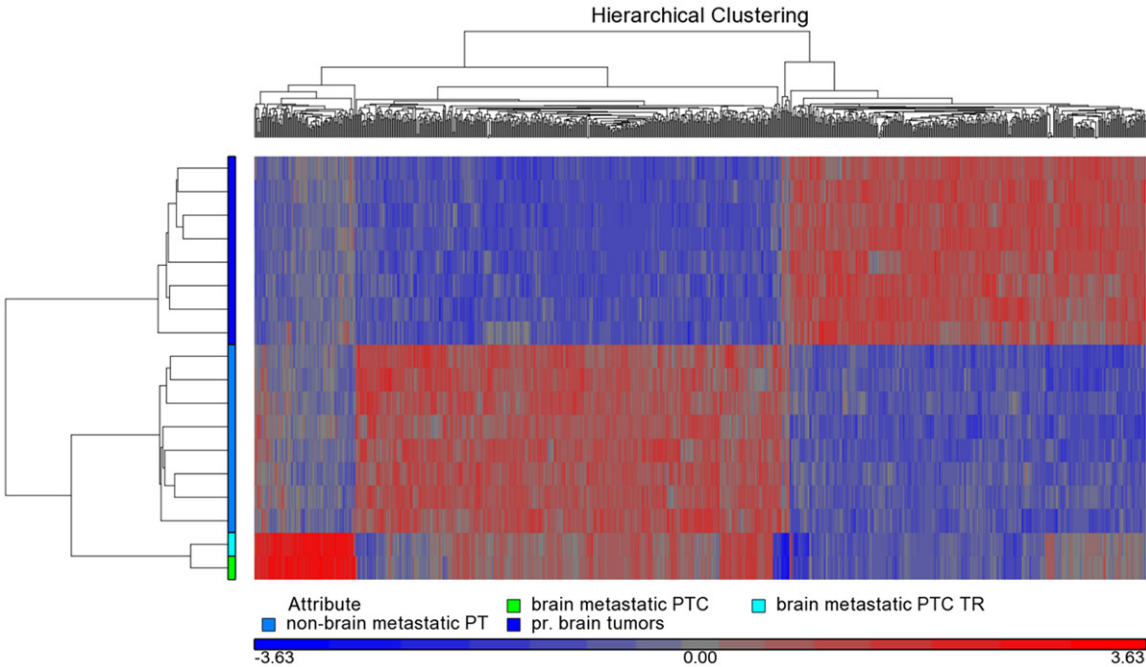
### *Genes differentially expressed in the brain metastasis and the TR vs. non-brain metastatic PTCs and primary brain tumors*

A detailed microarray expression analysis was performed on a rare brain metastasis from a PTC, including its TR, eight non-brain metastatic, stage III and IV PTCs and eight primary brain tumors (**Table 2**). The primary brain tumors were of meningioma histology and selected as described under Material and methods. Similarity of expression profiles of all 18 samples is illustrated by a distance related scale in a PCA 3D scatter plot (**Figure 3**). Hierarchical cluster analysis separately groups the brain metastatic PTC and the TR, from non-brain metastatic PTCs, and primary brain tumors (**Figure 4**). The 18 tumor samples served as basis to generate four differentially expressed comparison groups, i.e. brain metastatic PTC vs. non-brain metastatic PTCs, brain metastatic PTC (TR) vs. non-brain metastatic PTCs, brain metastatic PTC vs. primary brain tumors, and brain metastatic PTC (TR) vs. primary brain tumors. The top 95 differentially expressed probe sets, that





**Figure 3.** PCA 3D scatter plot as a dimensional, distance-related measure to display similarity of expression profiles of samples that are indicated by dots. Bounding ellipsoids are included for non-brain metastatic PTCs and primary brain tumors. Colors for samples/groups of samples as indicated in the color scheme legend.



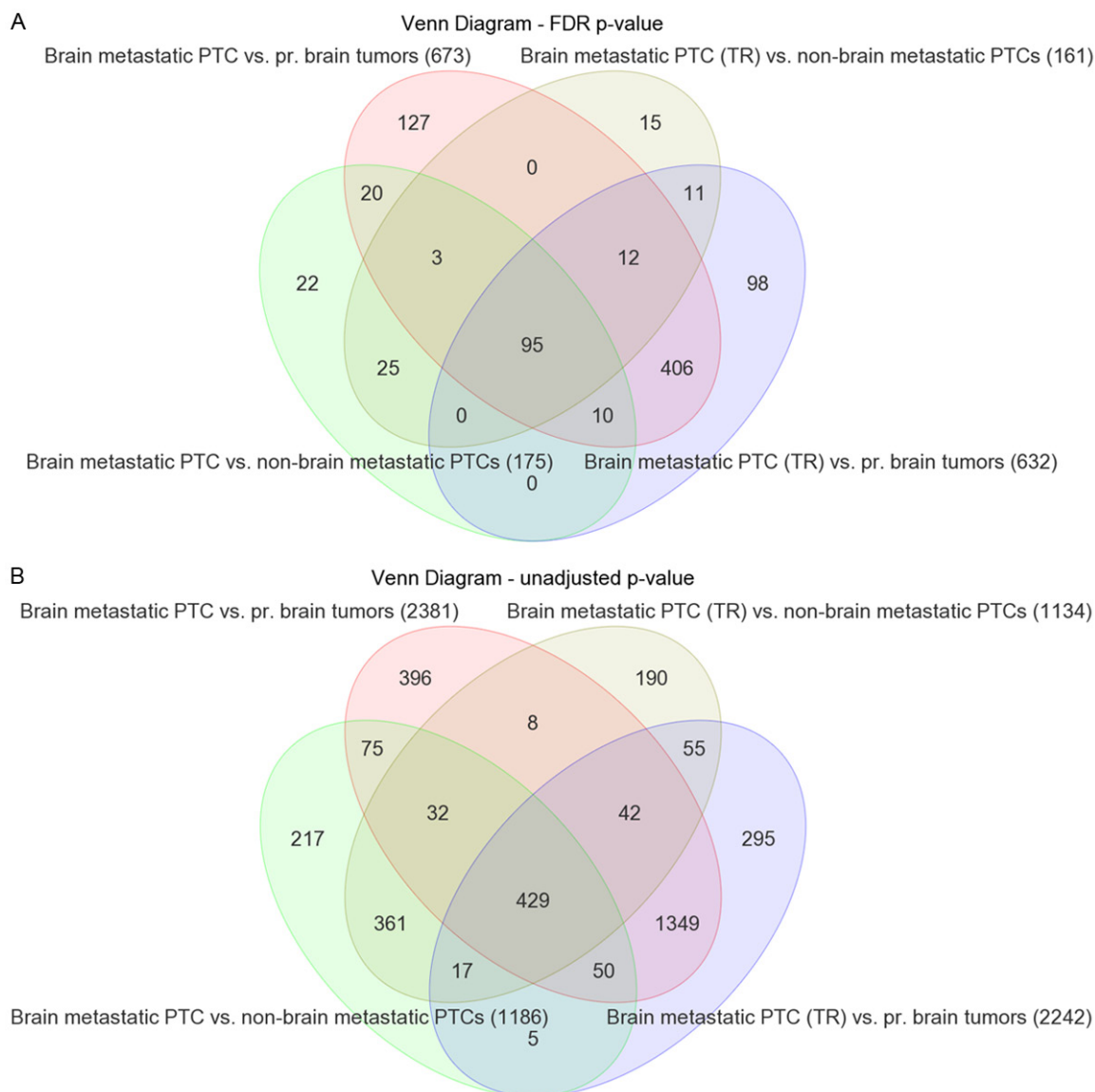
**Figure 4.** Hierarchical cluster analysis between the brain metastatic PTC, the TR, non-brain metastatic PTCs, and primary brain tumors. The brain metastatic PTC and the TR are clustering separately from the two other groups. Analysis is based on 796 differentially expressed probe sets ( $p$ -value < 0.0005). Colors for samples/groups of samples as indicated in the color scheme legend.

primarily distinguish the brain metastatic PTC from both, non-brain metastatic PTCs and pri-

mary brain tumors were those that intersect with all four comparison groups (**Figure 5A**,



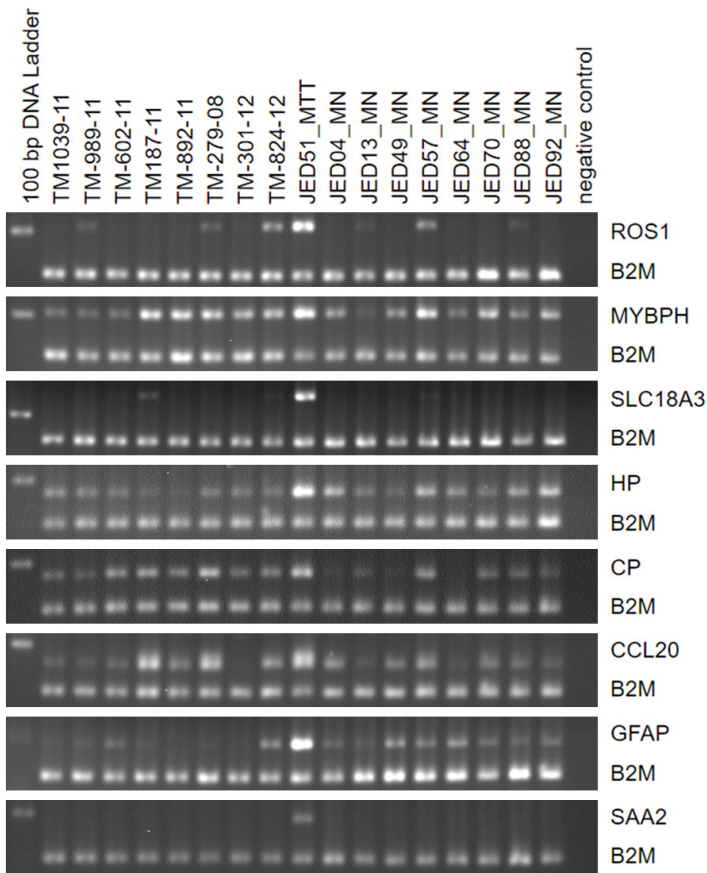
## Gene expression and biofunctions related to a brain metastasis from a PTC



**Figure 5.** Venn diagrams displaying differentially expressed probe sets that intersect or non-intersect between different comparison groups. A. Applying a FDR  $p$ -value  $< 0.05$  and  $FC > 2.0$  results in 95 differentially expressed probe sets ([Supplement Table 1](#)) that intersect between the four comparison groups brain metastatic PTC vs. non-brain metastatic PTCs, brain metastatic PTC (TR) vs. non-brain metastatic PTCs, brain metastatic PTC vs. primary brain tumors, and brain metastatic PTC (TR) vs. primary brain tumors. The 95 probe sets include 90 genes represented by one probe set each, 2 genes represented by two probe sets each, and one unmapped transcript. B. Applying the unadjusted  $p$ -value  $< 0.05$  and  $FC > 2.0$  results in 429 differentially expressed probe sets that intersect between the comparison groups as outlined under A ([Supplement Table 1](#)). Numbers of probe sets that are differentially expressed in each comparison group are given in parentheses.

[Supplement Table 1](#)). The 95 probe sets were in the vast majority comparably upregulated in the brain metastatic PTC. The encoded proteins/molecules represent various functional categories. These include the cytokines CCL20, CXCL1, CCL13, OSM, CXCL8, IL6, IL17C, CXCL2, IL1B, and IL32; proteins with receptor activity, e.g. ROS1, FPR2, IL1R2, and SIGLEC6; cyto-

skeletal and related proteins, e.g. MYBPH, GFAP, KRT17, ACTBL2, and TUBB3; enzymes including proteases and their inhibitors, e.g. XDH, PI3, NAPSA, FSTL5, SPINK14, TMPRSS3, and MMP7; and transporter proteins, e.g. SLC18A3, CP, CNTNAP5, AQP5, and SLC6A14. Molecules of various categories were, e.g. HP, SAA1, SAA2, SAA2-SAA4, DMBT1, ZER1,



**Figure 6.** Semiquantitative RT-PCR for *ROS1*, *MYBPH*, *SLC18A3*, *HP*, *CP*, *CCL20*, *GFAP*, and *SAA2* in the case series of eight thyroid tumors (TM-1039-11, TM-989-11, TM-602-11, TM-187-11, TM-892-11, TM-279-08, TM-301-12, and TM-824-12), the brain metastatic thyroid tumor (Jed51\_MTT) and eight primary brain tumors (Jed04\_MN, Jed13\_MN, Jed49\_MN, Jed57\_MN, Jed64\_MN, Jed70\_MN, Jed88\_MN, and Jed92\_MN). The genes rank among the top differentially expressed probe sets (Supplement Table 1). The PCR products of the interrogated genes have a size between 178-240 bp (Table 1). Product size of the internal reference gene *B2M* is 156 bp. Relative band densities of the PCR products for all eight genes compared to *B2M* is comparably highest for Jed51\_MTT. Some cases as e.g. Jed57\_MN express considerable amounts of *MYBPH* (~55%, compared to Jed51\_MTT), or TM-279-08 express considerable amounts of *CP* (~69%) and *CCL20* (~64%). Lane 1 contains the DNA ladder with the 200 bp band visible in the image fields and lane 19 contains the negative control reactions.

HSPA6, OTX2, RRAD, RAB7B, MIR146A, SBSN, and FAM83A. Eight differentially expressed genes, i.e. *ROS1*, *MYBPH*, *SLC18A3*, *HP*, *CP*, *CCL20*, and *GFAP* were subjected to semiquantitative RT-PCR that substantially confirmed microarray expression data (Figure 6).

*Biofunctional prediction analysis*

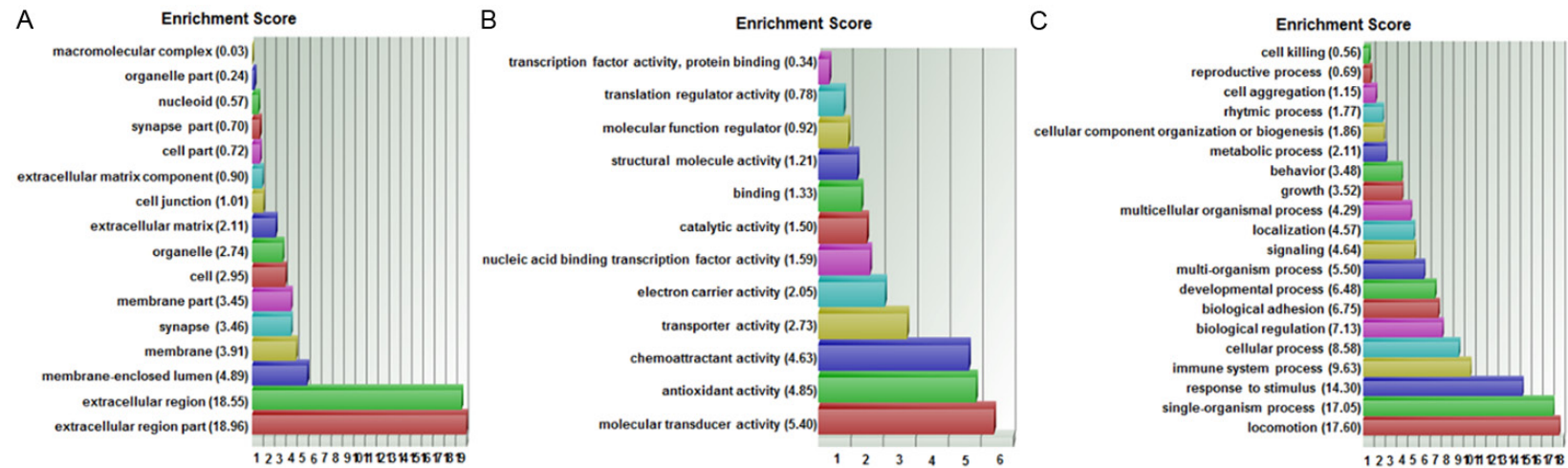
Biofunctional analysis was performed on the set of 429 differentially expressed probe sets ( $p$ -value < 0.05 and FC > 2) (Figure 5B,

Supplement Table 1). Functional groups that were significantly over-represented in different ontology categories are illustrated in a GO enrichment analysis (Figure 7). In the cellular component domain, the categories extracellular region part, extracellular region, and membrane-enclosed lumen were prevalent. In the molecular function domain, the most significantly related categories were molecular transducer activity, antioxidant activity, and chemoattractant activity. In the biological process domain, the prevalent categories were locomotion, single-organism process, and response to stimuli. The top canonical pathway was entitled granulocyte adhesion and diapedesis, illustrating molecular processes implicated in transendothelial migration (Table 3, Figure 8). Other top pathways were likewise related to inflammatory response and diseases. Network analysis identified as most significantly related upstream regulators lipopolysaccharide, the nuclear NFkB (complex), and the cytokines TNF, IL1A, and CSF2, otherwise known as GM-CSF (Table 3, Figure 9). Top networks under the category diseases & functions were entitled migration of cells, cell movement, cell survival, apoptosis, and proliferation of cells (Table 3, Figure 10).

*Genes shared between the brain metastasis and primary brain tumors*

To identify candidate genes that may support the brain metastasis to adapt and expand in the brain microenvironment, we selected (FDR  $p$ -value < 0.05 and FC > 2.0) in our data set for those probe sets that intersect between the comparison groups, brain metastatic PTC vs. non-brain metastatic PTCs, brain metastatic PTC (TR) vs. non-brain metastatic PTCs, and primary brain tumors vs. non-brain metastatic PTCs. Furthermore, we excluded from the intersecting probe sets those that were included in the list of 429 probe sets. The resulting probe

## Gene expression and biofunctions related to a brain metastasis from a PTC



**Figure 7.** GO enrichment analysis for the 429 differentially expressed probe sets. The functional categories are ranked according to their *p*-values. A. The categories extracellular region part, extracellular region, and membrane-enclosed lumen were most overrepresented in the cellular component domain. B. The most overrepresented categories in the molecular function domain were molecular transducer activity, antioxidant activity, and chemoattractant activity. C. The dominant categories in the biological process domain were locomotion, single-organism process, and response to stimulus.

**Table 3.** Top pathways and networks based on 429 differentially expressed probe sets

| Category                             | Brain metastatic PTC vs. non-brain metastatic PTCs |                                | Brain metastatic PTC vs. primary brain tumors |                                |
|--------------------------------------|--|--------------------------------|---|--------------------------------|
|                                      | p-value  | Overlap [%]/activation z-score | p-value                                       | Overlap [%]/activation z-score |
| Top canonical pathways               |  |                                |   |                                |
| Granulocyte adhesion and diapedesis  | 1.38E-09   | 11.4                           | 1.38E-09                                      | 11.4                           |
| Agranulocyte adhesion and diapedesis | 8.24E-07   | 8.9                            | 8.24E-07                                      | 8.9                            |
| Role of IL-17A in psoriasis          | 2.79E-06   | 38.5                           | 2.79E-06                                      | 38.5                           |
| LXR/RXR activation                   | 3.21E-06   | 10.0                           | 3.21E-06                                      | 10.0                           |
| Acute phase response signaling       | 4.04E-06   | 8.4                            | 4.04E-06                                      | 8.4                            |
| Top upstream regulators              |  |                                |   |                                |
| Lipopolysaccharide                   | 1.81E-23   | 6.382                          | 1.81E-23                                      | 6.734                          |
| TNF                                  | 2.82E-23   | 5.799                          | 2.82E-23                                      | 6.102                          |
| NFkB (complex)                       | 2.99E-22   | 5.477                          | 2.99E-22                                      | 5.477                          |
| IL1A                                 | 4.46E-20   | 4.668                          | 4.46E-20                                      | 5.016                          |
| CSF2                                 | 4.12E-18   | 4.729                          | 4.12E-18                                      | 4.729                          |
| Diseases & functions                 |  |                                |   |                                |
| Migration of cells                   | 9.77E-14   | 5.694                          | 9.77E-14                                      | 4.989                          |
| Cell movement                        | 1.48E-13   | 5.982                          | 1.48E-13                                      | 5.298                          |
| Cell survival                        | 3.24E-13   | 5.493                          | 3.24E-13                                      | 5.203                          |
| Apoptosis                            | 6.63E-13   | -0.923                         | 6.63E-13                                      | -2.397                         |
| Proliferation of cells               | 1.22E-12   | 4.191                          | 1.22E-12                                      | 4.063                          |

sets include *CASP1*, *CASP4*, and *C1R* which were comparably higher expressed and *CC2-D2B*, *RNY1P16*, *WDR72*, *LRRC2*, *ZHX2*, *CITED1*, and the noncoding and uncharacterized transcript AK128523 which were comparably lower expressed in the brain metastatic PTC.

## Discussion

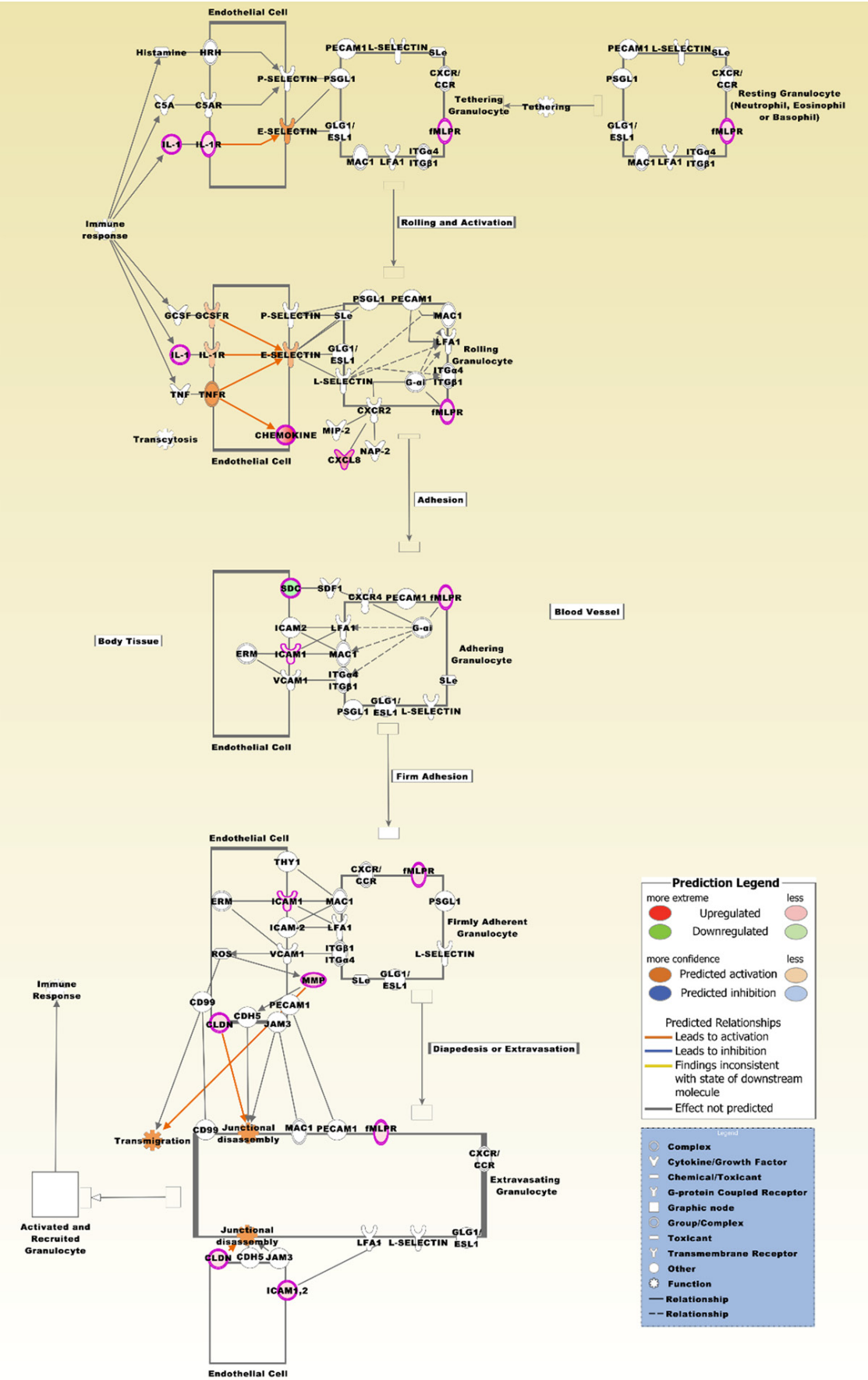
In contrast to melanoma, breast and lung cancer, which contribute to the majority of cancers with brain metastasis, brain metastatic PTCs are rare and presence of a PTC brain metastasis prior to detection of the primary thyroid tumor is exceptionally rare [19]. We present to our knowledge the first whole transcript expression profile of a brain metastasis from a PTC. Critical steps of the brain metastatic process as transmigration through the blood brain barrier (BBB) are not fully explored yet and depend on a number of factors as tissue type of tumor cells, cellular interactions and the time interval needed for extravasation [8, 9]. By comparing the expression profile of a brain metastasis with profiles of advanced stage, non-brain metastatic PTCs and with profiles of statistically sorted primary brain tumors, we selected for those differentially expressed candidate genes

that are most probably related to *in vivo* characteristics of the brain metastatic process. The *BRAF* mutational status of PTC metastases to the brain has only been reported for a small number of cases providing limited information to the clinical behavior of these metastases [20, 21]. A meta-analysis revealed that distant metastases from PTCs are not significantly associated with the *BRAF* mutational status [22]; however, a positive *BRAF* mutational status was more frequently observed in PTCs with a brain metastasis in comparison to other metastatic sites as soft tissue, lung, and retroperitoneum [20].

## Cytokines

CCL20 is a ligand for CCR6 and its expression is a proinflammatory signal, known to be upregulated in a number of cancer types. In SW1736 thyroid cancer cells, migration and invasion was induced by activation of CCR6 through CCL20 [23]. In addition, CCL20 stimulated expression and secretion of MMP3 and the nuclear translocation and activation of NFkB which is known to be implicated in a variety of cellular functions including cytokine activation and exertion of pro-tumorigenic activities. Of notice,





**Figure 8.** The top canonical pathway is entitled granulocyte adhesion and diapedesis. The pathway is based on the list of 429 differentially expressed probe sets that intersect between the four comparison groups (**Figure 2B**), and displaying the expression values derived from the two comparison groups, brain metastatic PTC vs. non-brain metastatic PTCs and brain metastatic PTC (TR) vs. non-brain metastatic PTCs (**Supplement Table 1**). Molecules that are comparably upregulated in the brain metastatic PTC include CCL2, CCL13, CCL18, CCL20, CCL22, CXCL1, CXCL2, CXCL8, CXCL14, CX3CL1, CLDN10, FPR2, IL1A, IL1B, IL1R2, ICAM1, and MMP7. SDC2 is comparably downregulated. A number of molecules from the probe sets are displayed under their group specific names, e.g. chemokines, CLDN, fMLPR, IL-1, MMP, and SDC. This pathway was also most significantly associated with the 95 probe sets ( $p$ -value 5.51E-08).

upregulation of CCL20 in endothelial cells that line specific zones of the BBB has been associated with a support for autoreactive T cells to cross the BBB regionally [24]. CCL20 was also included in the top scoring gene list derived from a comparison of parental breast cancer cell lines CN34 and MDA231 with their derivatives possessing brain metastatic behavior [25]. CXCL1 and CXCL2 are neutrophil chemoattractants. Overexpression of both chemokines in breast cancer cells increased survival of cancer cells at the metastatic sites [26]. In a rat model of soman-induced status epilepticus, CXCL1 expression was induced in neurons and endothelial cells [27]. An *in vitro* and *in vivo* study demonstrated that CCL2 expression from breast cancer cells and stroma attracts inflammatory monocytes that promotes metastasis of breast tumors [28]. CCL13 is the ligand of chemokine receptors CCR1, CCR2, CCR3, and CCR5. Although CCL13 is a critical factor in inflammatory diseases [29] its functions in cancer is not well defined. OSM is structurally related to IL6 and was found to inhibit thyroid peroxidase gene expression in porcine thyroid cell culture [30]. CXCL8, IL17, and IL6 were among a number of cytokines that were detected with increased levels upon neuroinflammatory stimulus in a 3D microfluidic chip model of the human BBB [31]. Furthermore, in SW480 and Caco-2 cells, proliferation, invasion, or epithelial-mesenchymal transition could be synergistically fostered by CXCL8 and CCL20 via the PI3K/AKT and ERK1/2 pathways [32]. GBM cells which were selected in a lung metastasis assay showed increased expression of IL6, IL8 and other factors known to be associated with unfavorable prognosis [33]. IL17C is preferentially expressed from non-immune cells and its expression was found to be comparably upregulated in the CNS of mice with induced autoimmune encephalomyelitis [34, 35]. In an *in vitro* BBB model, treatment with recombinant IL1B abolished BBB integrity by suppressing astrocytic SHH production and furthermore, led to

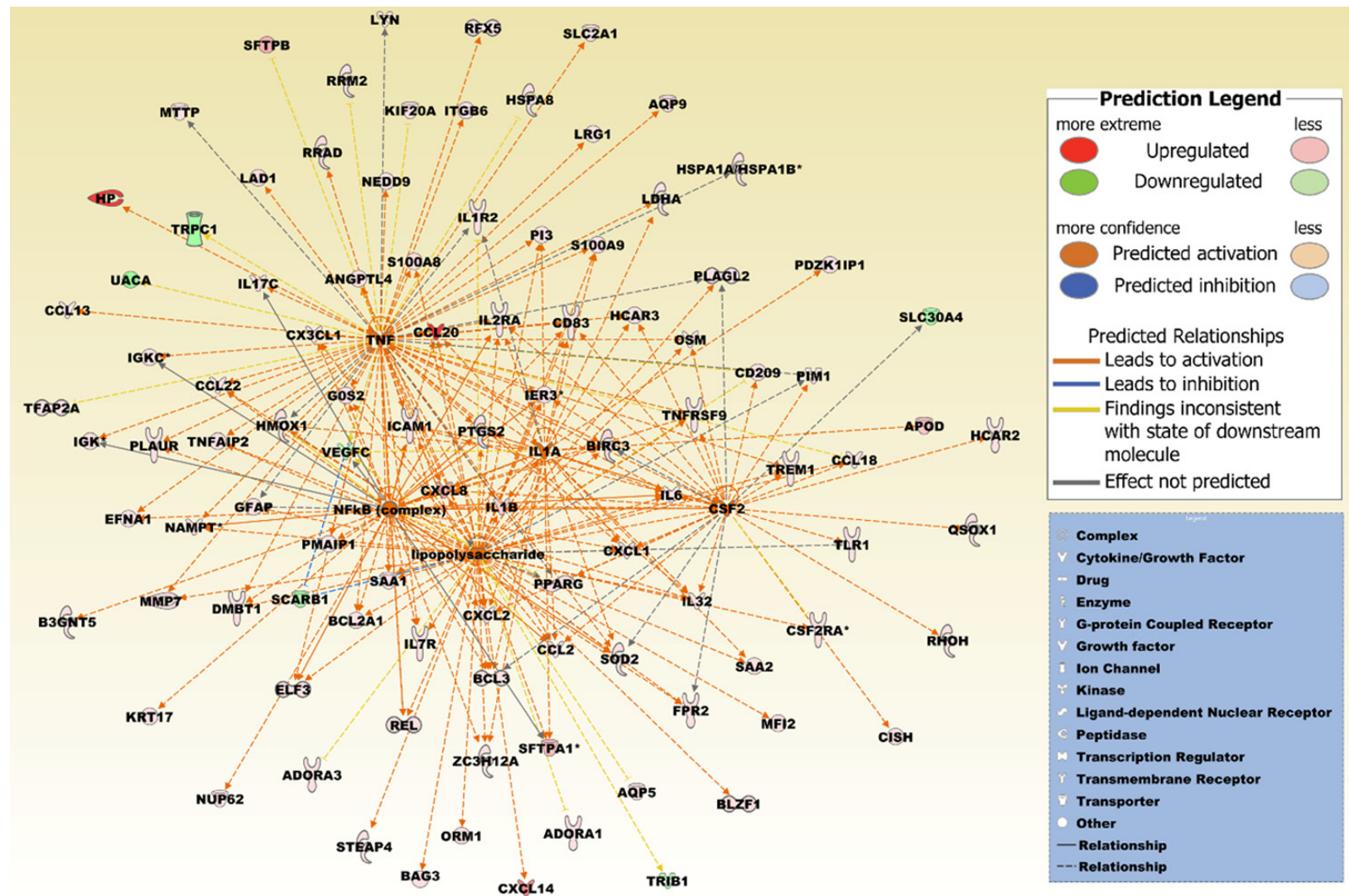
increased synthesis of CCL2, CCL20, and CXCL2 in astrocytes [36]. The proinflammatory cytokine IL32, alias NK4, is an established cancer associated factor that was demonstrated e.g. in cell culture experiments wherein a splice variant of IL32 promoted migration and invasion of breast cancer cells via the downstream VEGF/STAT3 pathway [37].

## Proteins with receptor activity

IL1R2 is a decoy receptor that interferes with the binding of IL1R1 to IL1A and IL1B. The receptor is known to be expressed in various cancer types [38]. ROS1 encodes a receptor tyrosine kinase with yet unknown ligand and it exhibits conserved relationship with ALK and the leukocyte tyrosine kinase LTK. Among other genes, upregulation of ROS1 was detected in GBM clones that were resistant to the EGFR inhibitor Gefitinib [39]. FPR2 is a G protein-coupled chemoattractant receptor [40]. *In vitro* and *in vivo* studies revealed that glioma cells overexpressing FPR showed increased motility and were more invasive than non-FPR overexpressing glioma cells [41]. SIGLEC6 is a cell membrane receptor containing an extracellular immunoglobulin domain for sialic acids binding and an intracellular immunoreceptor tyrosine-based inhibitory motif. Expression of SIGLEC6 in choriocarcinoma-derived BeWO cells resulted in decreased apoptosis and enhanced proliferation and invasiveness [42].

## Cytoskeletal and related proteins

MYBPH is a cytoskeletal protein that is involved in a number of cellular processes; however, its functions are not fully explored yet. Of notice, *in vitro* experiments demonstrated that MYBPH expression is positively regulated by TTF-1 and furthermore, MYBPH overexpression impairs actomyosin organization and acts as a negative factor for cell motility and migration of collective cells but not of single cells [43]. This latter observation can be of relevance in the context



**Figure 9.** A merged network based on the top five upstream regulators lipopolysaccharide, nuclear NFkB (complex) and the cytokines TNF, IL1A, and CSF2. IL1A is also included in the differentially expressed probe set list. Increased activation is predicted by a z-score > 2 (Table 3). The network is based on the list of 429 differentially expressed probe sets that intersect between the four comparison groups (Figure 5B), and reflecting the expression values derived from the two comparison groups, brain metastatic PTC vs. non-brain metastatic PTCs and brain metastatic PTC (TR) vs. non-brain metastatic PTCs (Supplement Table 1). Upregulated molecules include ADORA1, ADORA3, ANGPTL4, APOD, AQP5, AQP9, B3GNT5, BAG3, BCL2A1, BCL3, BIRC3, BLZF1, CCL13, CCL18, CCL2, CCL20, CCL22, CD209, CD83, CISH, CSF2RA, CX3CL1, CXCL1, CXCL14, CXCL2, CXCL8, DMBT1, EFNA1, ELF3, FPR2, GOS2, GFAP, HCAR2, HCAR3, HMOX1, HP, HSPA1A/HSPA1B, HSPA8, ICAM1,



IER3, IGK, IGKC, IL17C, IL1A, IL1B, IL1R2, IL2RA, IL32, IL6, IL7R, ITGB6, KIF20A, KRT17, LAD1, LDHA, LRG1, LYN, MFI2, MMP7, MTPP, NAMPT, NEDD9, NUP62, ORM1, OSM, PDZK1IP1, PI3, PIM1, PLAGL2, PLAUR, PMAIP1, PPARG, PTGS2, QSOX1, REL, RFX5, RHOH, RRAD, RRM2, S100A8, S100A9, SAA1, SAA2, SFTPA1, SFTPB, SLC2A1, SOD2, STEAP4, TFAP2A, TLR1, TNFAIP2, TNFRSF9, TREM1, and ZC3H12A. Downregulated molecules include SCARB1, SLC30A4, TRIB1, TRPC1, UACA, and VEGFC. The pathway was overlaid with the Molecule Activity Predictor to precalculate further molecular effects, as outlined in the prediction legend.

that the brain metastatic cells in our study harbored expression signatures related to granulocyte/agranulocyte adhesion and diapedesis processes. GFAP is an intermediate filament protein that is an established marker for a number of glial tumors [44]. Overexpression of KRT17 has been found in an IHC study to be associated with lymph node metastasis in PTCs [45]. Within the cytoskeleton structures, actin filaments form dynamic networks that can rapidly reorganize, determine cytokinesis, cell shape, and are mandatory for cell adhesion, migration, and invasion [46]. Overexpression of the ubiquitously expressed gene *ACTBL2*, alias kappa-actin, is associated with unfavorable prognosis in hepatocellular carcinoma and its induced overexpression in hepatoma cells led to enhanced serum-independent cell proliferation and anchorage-independent colony formation [47]. Expressional dataset analysis detected overexpression of the beta tubulin protein TUBB3 in brain metastases of breast cancers but not in the primary tumors [48]. Furthermore, knockdown of TUBB3 in brain metastatic breast cancer cells reduced their metastatic capacity in mice which led to increased survival of the rodents.

### *Enzymes including proteases and their inhibitors*

*XDH* encodes a molybdoflavin enzyme that catalyzes the oxidative reactions of hypoxanthine to xanthine and subsequently of xanthine to uric acid. The role of the enzyme in cancer has not been thoroughly elucidated; however, *XDH* expression has been identified by mass spectrometry in bovine brain capillary endothelial cells (BCECs) exhibiting functional BBB properties that were induced by co-cultured glial cells, whereas mono-cultured BCECs with impaired BBB properties did not express detectable *XDH* [49]. *PI3*, also known as elafin, is a serine protease inhibitor that is synthesized and secreted locally at the site of injury in response to primary cytokines such as *IL1* and *TNF* [50]. In an experimental anti-angiogenesis *in vivo* model system, *PI3* was upregulated in GBM and its

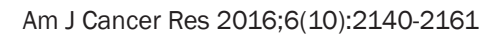
upregulation was found to be associated with poor prognosis in GBM patients [51]. *NAPSA* encodes an aspartic protease that is used as an IHC marker for subclassification of lung tumors. In thyroid cancer, IHC expression of *NAPSA* was detected in a subset of poorly differentiated thyroid carcinomas and anaplastic carcinomas but only in a vast minority of PTCs [52]. *FSTL5* is an enzyme modulator of the follistatin family and the secretory glycoprotein was identified in a microarray expression and IHC study as a marker of unfavourable prognosis in different subtypes of medulloblastomas [53]. The function of *SPINK14* in cancer is barely known but the protease inhibitor was listed among the top downregulated genes in HepG2 cells upon treatment with the *EZH2* inhibitor *GSK343* [54]. *TMPRSS3* is a type II transmembrane serine protease that, when overexpressed in ovarian A2780 cells, promotes their proliferation, invasion, and migration and an IHC study revealed that *TMPRSS3* expression is an unfavorable prognostic factor in breast cancer patients [55, 56]. *MMP7* is a secreted matrix metalloproteinase. *In vitro* assays in prostate cancer cells demonstrated that the proteinase sufficiently digests perlecan, a core component of basement membranes, and by this facilitates cell invasion [57].

### *Transporter proteins*

The vesicular acetylcholine transporter *SLC18A3* encodes a transmembrane molecule that loads acetylcholine into secretory vesicles in presynaptic nerve terminals. An RT-PCR assay demonstrated that induction of differentiation of human neuroblastoma cell line LAN-5 by retinoic acid resulted in a number of deregulated genes under which *SLC18A3* was shown to be initially upregulated [58]. *CP* owns ferroxidase activity and it is implicated in supporting iron transport across the BBB. In an *in vitro* BBB model system, expression of *CP* in C6 glioma cells was stimulated by *IL1B* and *IL6* that were expressed from neighboring brain microvascular endothelial cells [59]. According to microarray expression data, *CNTNAP5*, which is a



## 2155



**Figure 10.** The top five merged networks under the category diseases & functions were entitled migration of cells, cell movement, cell survival, apoptosis, and proliferation of cells. Increased activation is predicted by a z-score > 2 (Table 3). The network is based on the list of 429 differentially expressed probe sets that intersect between the four comparison groups (Figure 5B), and reflecting the expression values derived from the two comparison groups, brain metastatic PTC vs. non-brain metastatic PTCs and brain metastatic PTC (TR) vs. non-brain metastatic PTCs (Supplement Table 1). Upregulated molecules include ADORA1, ADORA3, ADRA1B, ANGPTL4, APOD, AQP5, AQP9, BAG3, BCL2A1, BCL3, BIRC3, BLZF1, BNIP3, BUB1, CCL13, CCL18, CCL2, CCL20, CCL22, CCT5, CD209, CD83, CDC6, CDC7, CDK1, CDK5, CISH, COL11A1, CR1, CSF2RA, CTSE, CX3CL1, CXCL1, CXCL14, CXCL2, CXCL8, DAB2, DACH1, DBF4, DEGS1, DGKB, DNAJB1, EFNA1, EGF, EGLN3, ELF3, ETHE1, ETV6, EZH2, FAM83A, FPR2, GOS2, GAREM1, GFAP, HCAR2, HILPDA, HMOX1, HP, HSPA1A/HSPA1B, HSPA8, ICAM1, IER3, IGF2BP3, IGHM, IGK, IGKC, IL17C, IL1A, IL1B, IL27RA, IL2RA, IL2RB, IL32, IL6, IL7R, ITGB6, KIF14, KIF20A, KPNA2, LDHA, LMNB1, LYN, MAP3K1, MFI2, MGLL, MMP7, NAMPT, NDC80, NEDD9, NNAT, NR2F1, NUF2, NUP62, ORM1, OSM, OTX2, PDE4DIP, PDK1, PDZK1IP1, PI3, PIM1, PKM, PLAUR, PMAIP1, PON2, PPARG, PPP1R1B, PROM1, PROX1, PTGS2, PTP4A3, PTTG1, QSOX1, RASSF4, RASSF5, REL, ROS1, RRAD, RRM2, S100A8, S100A9, SAA1, SFTPA1, SIGLEC6, SIX1, SLC18A3, SLC22A18, SLC2A1, SMYD3, SNRPE, SOD2, SRPX2, TCP1, TFAP2A, TLR1, TNFAIP2, TNFRSF9, TREM1, TRIB2, TUBB3, UNC5CL, VSTM2L, XDH, XPR1, and ZIC1. Downregulated molecules include ABL1, GNG7, HHEX, INVS, MAGEH1, PARK2, PLCD1, PRKCQ, RGN, SCARB1, SDC2, TENM1, TRIB1, TRPC1, UACA, VEGFC, and WASF3. The pathway was overlaid with the Molecule Activity Predictor to precalculate further molecular effects, as outlined in the prediction legend.

member of the neurexin family and associated with potassium channels is comparably high expressed in a number of brain cancers including medulloblastoma, pilocytic astrocytoma, and cerebellar tumors [60]. In prostate cancer, the water channel protein AQP5 was identified as an unfavorable prognostic marker and cell culture experiments indicated that siRNA knockdown of AQP5 inhibited proliferation and migration of prostate cancer cells [61].

#### *Molecules of various categories*

HP has been found with increased serum levels by quantitative protein analysis in patients with brain metastatic lung cancer [62]. Furthermore, *in vitro* and *in vivo* studies identified HP as a key mediator of metastatic cell homing, fostering invasion, migration, including transendothelial migration, and proliferation of cancer cells [63]. SAA proteins are the major acute phase response molecules and considered as a family of apolipoproteins. SAA2-SAA4 is transcribed as a readthrough between the adjunct SAA2 and SAA4 genes. Overexpression of isoforms SAA1 and SAA2 was found in sera of lung cancer patients and in lung carcinoma cells that metastasized and settled in the lung of a mouse model [64]. Furthermore, recombinant SAA1 differentially affected cell migration and invasion in two tested glioma cell lines [65]. DMBT1 is a member of the scavenger receptor cysteine-rich superfamily and it was initially identified as a gene deleted in a number of medulloblastoma and GBM samples and cell lines [66]. Detailed *in vitro* and *in vivo* studies established DMBT1 as a critical vascular extracellular matrix protein that promotes endothe-

lial cell adhesion, migration, proliferation, and angiogenesis [67]. ZER1, that was in our study comparably downregulated in the brain metastatic PTC, encodes a subunit of an E3 ubiquitin ligase complex. A microarray study in bladder cancer identified, among other genes, upregulation of ZER1 at tumor stage Ta-T1; however, its downregulation at stage T1-T2 [68]. Upon heat induction, heat shock protein HSPA6 has been identified in centrioles that are known to have critical functions in cellular polarity and migration processes during neuronal differentiation [69]. OTX2 encodes a homeobox transcription factor and is frequently gained in non-Shh/non-Wnt medulloblastomas. *In vitro* and *in vivo* experiments demonstrated that OTX2 overexpression promotes cell proliferation, whereas its knockdown reduces tumorigenicity of cells [70]. RRAD is a member of the (Rem/Rem2, Gem, Kir) RGK subfamily of the Ras family of small GTPases, sharing in its GTPase domain a ~35% identity with HRAS and other small GTPases. Overexpression of RRAD in primary GBM is associated with poor prognosis [71]. Furthermore, cell culture experiments in GBM LN229 cells demonstrated that RRAD, by inducing EGF, enhances STAT3 activation. Furthermore, immunoprecipitation showed that RRAD physically interacts with EGFR and *in vitro* and *in vivo* studies demonstrated that RRAD enhances colony formation and cell migration as well as tumor growth in nude mice. Downregulation of RRAD by siRNA treatment resulted in loss of expression of the stemness-regulating genes OCT4, NANOG, and SOX2 as well as in sensitizing of otherwise temozolomide-resistant LN229 clones. The small GTPase Rab7b is known to be involved in retrograde

transport of a number of sorting receptors and implicated in cell migration by actin cytoskeletal remodelling [72]. In a spinal cord injury rat model, MiR146A was one of the key miRNAs that was upregulated at the injury site over a longer time period and cell culture experiments indicated that MIR146A is a regulator of inflammation in glial cells [73, 74]. SBSN is known as an invasion promoting protein that was identified in a proteomics study in the secretome of a GBM cell line that does not express EGFR and PTEN and in GBM derivate cells that have induced expression of both, EGFR and PTEN [75]. In mouse tumor endothelial cells, siRNA depletion of SBSN inhibited migration and tube formation capacity [76]. The functional properties of FAM83A are less known, however, its overexpression in breast cancer cells increased proliferation and invasion and augmented EGFR resistance to tyrosine kinase inhibitors [77]. Moreover, independently of an upstream EGF/EGFR activation, FAM83A overexpression resulted in activation of CRAF and PI3K p85 which are known upstream activators of ERK1/2 and AKT. Conversely, FAM83A depletion by siRNA resulted in delayed tumor growth of a xenograft tumor model and metadata analysis demonstrated that high FAM83A expression correlates with unfavorable prognosis in breast cancer patients.

*Probe sets differentially expressed in the brain metastatic PTC, the TR, and primary brain tumors vs. non-brain metastatic PTCs*

C1R is a serine protease of the complement system and an activator of C1S that is known to enhance tumorigenic invasion and migration by extracellular matrix disintegration [78]. CASP1 and CASP4 are effector caspases that are involved in caspase activation and regulation of inflammatory processes [79]. Comparably highest RNA expression levels for WDR72, which is a critical factor in calcium transport, have been found in kidney and thyroid tissues which may support our results showing lower expression of WDR72 in the brain metastatic PTC and primary brain tumors [80]. The function of CC2D2B, especially in cancer, is virtually unknown; however, microarray expression data indicated that CC2D2B is a top upregulated gene in PTCs which may also be a support for our results of comparably lower expression of the factor in the brain metastasis and primary brain tumors

[60]. Similarly, *CITED1* which encodes a CREB-binding protein/p300-interacting transactivator was identified in a microarray expression study as an upregulated gene in PTCs [81]. ZHX2 is a zinc finger and homeobox containing factor. Induced expression of ZHX2 in xenograft tumors resulted in reduced tumor growths [82].

In conclusion, whole transcript expression profiling identified candidate genes including a number of cytokines, and biofunctions, notably the granulocyte adhesion and diapedesis pathway, associated with a brain metastasis of a PTC, suggesting an inherited expression profile related to the brain metastatic process.

## Acknowledgements

This study was supported by King Abdulaziz City for Science and Technology (KACST) grant AT-32-98 and KACST Technology Innovation Center in Personalized Medicine grant 13-CIPM-07. We thank Alaa Alamdi, Reem Alotibi, Nadia Baqtian, Ohoud Subhi, Manal Shabaat, Ishaq Khan, Mona Al-Omary, Nawal Madkhali, Lobna Siraj Mira, Maha Al-Quaiti, Fai Ashgan, Alaa Ghazi Almasri, Sabrin Bukhari, and Shireen Hussain for excellent technical assistance.

## Disclosure of conflict of interest

None.

## Abbreviations

aCGH, array comparative genomic hybridization; BBB, blood brain barrier; FC, fold change; FDR, false discovery rate; GO, gene ontology; GBM, glioblastoma multiforme; IHC, immunohistochemistry; FVPTC, follicular variant of PTC; PCA, principal component analysis; PTC, papillary thyroid carcinoma; TR, technical replicate.

**Address correspondence to:** Dr. Hans-Juergen Schulten, Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah 21589, Saudi Arabia. E-mail: hschulten@kau.edu.sa

## References

- [1] Zecchin D, Boscaro V, Medico E, Barault L, Martini M, Arena S, Cancelliere C, Bartolini A, Crowley EH, Bardelli A, Gallicchio M and Di Nicolantonio F. BRAF V600E is a determinant of sensitivity to proteasome inhibitors. *Mol Cancer Ther* 2013; 12: 2950-2961.



- [2] Schulten HJ, Alotibi R, Al-Ahmadi A, Ata M, Karim S, Huwait E, Gari M, Al-Ghamdi K, Al-Mashat F, Al-Hamour O, Al-Qahtani MH and Al-Maghrabi J. Effect of BRAF mutational status on expression profiles in conventional papillary thyroid carcinomas. *BMC Genomics* 2015; 16 Suppl 1: S6.
- [3] Dadu R and Cabanillas ME. Optimizing therapy for radioactive iodine-refractory differentiated thyroid cancer: current state of the art and future directions. *Minerva Endocrinol* 2012; 37: 335-356.
- [4] Tahmasebi FC, Farmer P, Powell SZ, Aldape KD, Fuller GN, Patel S, Hollis P, Chalif D, Eisenberg MB and Li JY. Brain metastases from papillary thyroid carcinomas. *Virchows Arch* 2013; 462: 473-480.
- [5] Tsuda K, Tsurushima H, Takano S, Tsuboi K and Matsumura A. Brain metastasis from papillary thyroid carcinomas. *Mol Clin Oncol* 2013; 1: 817-819.
- [6] Chiu AC, Delpassand ES and Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab* 1997; 82: 3637-3642.
- [7] Shen Y, Ruan M, Luo Q, Yu Y, Lu H, Zhu R and Chen L. Brain metastasis from follicular thyroid carcinoma: treatment with sorafenib. *Thyroid* 2012; 22: 856-860.
- [8] Singh M, Manoranjan B, Mahendram S, McFarlane N, Venugopal C and Singh SK. Brain metastasis-initiating cells: survival of the fittest. *Int J Mol Sci* 2014; 15: 9117-9133.
- [9] Wilhelm I, Molnar J, Fazakas C, Hasko J and Krizbai IA. Role of the blood-brain barrier in the formation of brain metastases. *Int J Mol Sci* 2013; 14: 1383-1411.
- [10] AJCC Cancer Staging Manual. Edited by Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. New York: Springer; 2010.
- [11] Schulten HJ, Hussein D, Al-Adwani F, Karim S, Al-Maghrabi J, Al-Sharif M, Jamal A, Al-Ghamdi F, Baeesa SS, Bangash M, Chaudhary A and Al-Qahtani M. Microarray Expression Data Identify DCC as a Candidate Gene for Early Meningioma Progression. *PLoS One* 2016; 11: e0153681.
- [12] Schneider CA, Rasband WS and Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods* 2012; 9: 671-675.
- [13] Schulten HJ, Salama S, Al-Mansouri Z, Alotibi R, Al-Ghamdi K, Al-Hamour OA, Sayadi H, Al-Aradati H, Al-Johari A, Huwait E, Gari M, Al-Qahtani MH and Al-Maghrabi J. BRAF mutations in thyroid tumors from an ethnically diverse group. *Hered Cancer Clin Pract* 2012; 10: 10.
- [14] Schulten HJ, Al-Mansouri Z, Baghallab I, Bagatian N, Subhi O, Karim S, Al-Aradati H, Al-Mutawa A, Johary A, Meccawy AA, Al-Ghamdi K, Al-Hamour O, Al-Qahtani M and Al-Maghrabi J. Comparison of microarray expression profiles between follicular variant of papillary thyroid carcinomas and follicular adenomas of the thyroid. *BMC Genomics* 2015; 16 Suppl 1: S7.
- [15] Schulten HJ, Alotibi R, Al-Ahmadi A, Ata M, Karim S, Huwait E, Gari M, Al-Ghamdi K, Al-Mashat F, Al-Hamour O, Al-Qahtani M and Al-Maghrabi J. Effect of BRAF mutational status on expression profiles in conventional papillary thyroid carcinomas. *BMC Genomics* 2015; 16 Suppl 1: S6.
- [16] Mi H, Poudel S, Muruganujan A, Casagrande JT and Thomas PD. PANTHER version 10: expanded protein families and functions, and analysis tools. *Nucleic Acids Res* 2016; 44: D336-342.
- [17] Schulten HJ, Al-Mansouri Z, Baghallab I, Bagatian N, Subhi O, Karim S, Al-Aradati H, Al-Mutawa A, Johary A, Meccawy AA, Al-Ghamdi K, Al-Hamour O, Al-Qahtani MH and Al-Maghrabi J. Comparison of microarray expression profiles between follicular variant of papillary thyroid carcinomas and follicular adenomas of the thyroid. *BMC Genomics* 2015; 16 Suppl 1: S7.
- [18] Kramer A, Green J, Pollard J Jr and Tugendreich S. Causal analysis approaches in Ingenuity Pathway Analysis. *Bioinformatics* 2014; 30: 523-530.
- [19] Al-Dhahri SF, Al-Amro AS, Al-Shakwer W and Terkawi AS. Cerebellar mass as a primary presentation of papillary thyroid carcinoma: case report and literature review. *Head Neck Oncol* 2009; 1: 23.
- [20] El-Osta H, Falchook G, Tsimberidou A, Hong D, Naing A, Kim K, Wen S, Janku F and Kurzrock R. BRAF mutations in advanced cancers: clinical characteristics and outcomes. *PLoS One* 2011; 6: e25806.
- [21] Capper D, Berghoff AS, Magerle M, Ilhan A, Wohrer A, Hackl M, Pichler J, Pusch S, Meyer J, Habel A, Petzelbauer P, Birner P, von Deimling A and Preusser M. Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. *Acta Neuropathol* 2012; 123: 223-233.
- [22] Tufano RP, Teixeira GV, Bishop J, Carson KA and Xing M. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. *Medicine (Baltimore)* 2012; 91: 274-286.
- [23] Zeng W, Chang H, Ma M and Li Y. CCL20/CCR6 promotes the invasion and migration of thyroid cancer cells via NF-kappa B signaling-induced MMP-3 production. *Exp Mol Pathol* 2014; 97: 184-190.
- [24] Arima Y, Harada M, Kamimura D, Park JH, Kawano F, Yull FE, Kawamoto T, Iwakura Y, Betz UA, Marquez G, Blackwell TS, Ohira Y, Hirano T and Murakami M. Regional neural activation



- defines a gateway for autoreactive T cells to cross the blood-brain barrier. *Cell* 2012; 148: 447-457.
- [25] Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA and Massague J. Genes that mediate breast cancer metastasis to the brain. *Nature* 2009; 459: 1005-1009.
- [26] Acharyya S, Oskarsson T, Vanharanta S, Mal-ladi S, Kim J, Morris PG, Manova-Todorova K, Leversha M, Hogg N, Seshan VE, Norton L, Brogi E and Massagué J. A CXCL1 paracrine network links cancer chemoresistance and metastasis. *Cell* 2012; 150: 165-178.
- [27] Johnson EA, Dao TL, Guignet MA, Geddes CE, Koemeter-Cox AI and Kan RK. Increased expression of the chemokines CXCL1 and MIP-1alpha by resident brain cells precedes neutrophil infiltration in the brain following prolonged soman-induced status epilepticus in rats. *J Neuroinflammation* 2011; 8: 41.
- [28] Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, Kaiser EA, Snyder LA and Pollard JW. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* 2011; 475: 222-225.
- [29] Mendez-Enriquez E and Garcia-Zepeda EA. The multiple faces of CCL13 in immunity and inflammation. *Inflammopharmacology* 2013; 21: 397-406.
- [30] Isozaki O, Tsushima T, Miyakawa M, Emoto N, Demura H, Arai M and Sato-Nozoe Y. Oncostatin M: a new potent inhibitor of iodine metabolism inhibits thyroid peroxidase gene expression but not DNA synthesis in porcine thyroid cells in culture. *Thyroid* 1997; 7: 71-77.
- [31] Herland A, van der Meer AD, FitzGerald EA, Park TE, Sleeboom JJ and Ingber DE. Distinct Contributions of Astrocytes and Pericytes to Neuroinflammation Identified in a 3D Human Blood-Brain Barrier on a Chip. *PLoS One* 2016; 11: e0150360.
- [32] Cheng XS, Li YF, Tan J, Sun B, Xiao YC, Fang XB, Zhang XF, Li Q, Dong JH, Li M, Qian HH, Yin ZF and Yang ZB. CCL20 and CXCL8 synergize to promote progression and poor survival outcome in patients with colorectal cancer by collaborative induction of the epithelial-mesenchymal transition. *Cancer Lett* 2014; 348: 77-87.
- [33] Xie Q, Thompson R, Hardy K, DeCamp L, Berghuis B, Sigler R, Knudsen B, Cottingham S, Zhao P, Dykema K, Cao B, Resau J, Hay R and Vande Woude GF. A highly invasive human glioblastoma pre-clinical model for testing therapeutics. *J Transl Med* 2008; 6: 77.
- [34] Waisman A, Hauptmann J and Regen T. The role of IL-17 in CNS diseases. *Acta Neuropathol* 2015; 129: 625-637.
- [35] Chang SH, Reynolds JM, Pappu BP, Chen G, Martinez GJ and Dong C. Interleukin-17C promotes Th17 cell responses and autoimmune disease via interleukin-17 receptor E. *Immunity* 2011; 35: 611-621.
- [36] Wang Y, Jin S, Sonobe Y, Cheng Y, Horiuchi H, Parajuli B, Kawanokuchi J, Mizuno T, Takeuchi H and Suzumura A. Interleukin-1beta induces blood-brain barrier disruption by downregulating Sonic hedgehog in astrocytes. *PLoS One* 2014; 9: e110024.
- [37] Park JS, Choi SY, Lee JH, Lee M, Nam ES, Jeong AL, Lee S, Han S, Lee MS, Lim JS, Yoon do Y, Kwon Y and Yang Y. Interleukin-32beta stimulates migration of MDA-MB-231 and MCF-7 cells via the VEGF-STAT3 signaling pathway. *Cell Oncol (Dordr)* 2013; 36: 493-503.
- [38] Liu X, Min L, Duan H, Shi R, Zhang W, Hong S and Tu C. Short hairpin RNA (shRNA) of type 2 interleukin-1 receptor (IL1R2) inhibits the proliferation of human osteosarcoma U-2 OS cells. *Med Oncol* 2015; 32: 364.
- [39] Aljohani H, Koncar RF, Zarzour A, Park BS, Lee SH and Bahassi el M. ROS1 amplification mediates resistance to gefitinib in glioblastoma cells. *Oncotarget* 2015; 6: 20388-20395.
- [40] Huang J, Chen K, Gong W, Zhou Y, Le Y, Bian X and Wang JM. Receptor "hijacking" by malignant glioma cells: a tactic for tumor progression. *Cancer Lett* 2008; 267: 254-261.
- [41] Huang J, Chen K, Chen J, Gong W, Dunlop NM, Howard OM, Gao Y, Bian XW and Wang JM. The G-protein-coupled formylpeptide receptor FPR confers a more invasive phenotype on human glioblastoma cells. *Br J Cancer* 2010; 102: 1052-1060.
- [42] Rumer KK, Post MD, Larivee RS, Zink M, Uyenishi J, Kramer A, Teoh D, Bogart K and Winn VD. Siglec-6 is expressed in gestational trophoblastic disease and affects proliferation, apoptosis and invasion. *Endocr Relat Cancer* 2012; 19: 827-840.
- [43] Hosono Y, Yamaguchi T, Mizutani E, Yanagisawa K, Arima C, Tomida S, Shimada Y, Hiraoka M, Kato S, Yokoi K, Suzuki M and Takahashi T. MYBPH, a transcriptional target of TTF-1, inhibits ROCK1, and reduces cell motility and metastasis. *EMBO J* 2012; 31: 481-493.
- [44] Goyal R, Mathur SK, Gupta S, Goyal R, Kumar S, Batra A, Hasija S and Sen R. Immunohistochemical expression of glial fibrillary acidic protein and CAM5.2 in glial tumors and their role in differentiating glial tumors from metastatic tumors of central nervous system. *J Neurosci Rural Pract* 2015; 6: 499-503.
- [45] Kim HS, Lee JJ, Do SI, Kim K, Do IG, Kim DH, Chae SW and Sohn JH. Overexpression of cytokeratin 17 is associated with the development of papillary thyroid carcinoma and the pres-

- ence of lymph node metastasis. *Int J Clin Exp Pathol* 2015; 8: 5695-5701.
- [46] Simiczyjew A, Mazur AJ, Popow-Wozniak A, Malicka-Blaszkiwicz M and Nowak D. Effect of overexpression of beta- and gamma-actin isoforms on actin cytoskeleton organization and migration of human colon cancer cells. *Histochem Cell Biol* 2014; 142: 307-322.
- [47] Chang KW, Chou A, Lee CC, Yeh C, Lai MW, Yeh TS, Chen TC, Liang KH and Yeh CT. Overexpression of kappa-actin alters growth properties of hepatoma cells and predicts poor postoperative prognosis. *Anticancer Res* 2011; 31: 2037-2044.
- [48] Kanojia D, Morshed RA, Zhang L, Miska JM, Qiao J, Kim JW, Pytel P, Balyasnikova IV, Lesniak MS and Ahmed AU. betaIII-Tubulin Regulates Breast Cancer Metastases to the Brain. *Mol Cancer Ther* 2015; 14: 1152-1161.
- [49] Cantu-Medellin N and Kelley EE. Xanthine oxidoreductase-catalyzed reduction of nitrite to nitric oxide: insights regarding where, when and how. *Nitric Oxide* 2013; 34: 19-26.
- [50] Sallenave JM. The role of secretory leukocyte proteinase inhibitor and elafin (elastase-specific inhibitor/skin-derived antileukoprotease) as alarm antiproteases in inflammatory lung disease. *Respir Res* 2000; 1: 87-92.
- [51] Saidi A, Javerzat S, Bellahcene A, De Vos J, Bello L, Castronovo V, Deprez M, Loiseau H, Bikfalvi A and Hagedorn M. Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. *Int J Cancer* 2008; 122: 2187-2198.
- [52] Chernock RD, El-Mofty SK, Becker N and Lewis JS Jr. Napsin A expression in anaplastic, poorly differentiated, and micropapillary pattern thyroid carcinomas. *Am J Surg Pathol* 2013; 37: 1215-1222.
- [53] Remke M, Hielscher T, Korshunov A, Northcott PA, Bender S, Kool M, Westermann F, Benner A, Cin H, Ryzhova M, Sturm D, Witt H, Haag D, Toedt G, Wittmann A, Schottler A, von Bueren AO, von Deimling A, Rutkowski S, Scheurlen W, Kulozik AE, Taylor MD, Lichter P and Pfister SM. FSTL5 is a marker of poor prognosis in non-WNT/non-SHH medulloblastoma. *J Clin Oncol* 2011; 29: 3852-3861.
- [54] Liu TP, Hong YH, Tung KY and Yang PM. In silico and experimental analyses predict the therapeutic value of an EZH2 inhibitor GSK343 against hepatocellular carcinoma through the induction of metallothionein genes. *Oncoscience* 2016; 3: 9-20.
- [55] Zhang D, Qiu S, Wang Q and Zheng J. TM-PRSS3 modulates ovarian cancer cell proliferation, invasion and metastasis. *Oncol Rep* 2016; 35: 81-88.
- [56] Rui X, Li Y, Jin F and Li F. TM-PRSS3 is a novel poor prognostic factor for breast cancer. *Int J Clin Exp Pathol* 2015; 8: 5435-5442.
- [57] Grindel BJ, Martinez JR, Pennington CL, Muldoon M, Stave J, Chung LW and Farach-Carson MC. Matrilysin/matrix metalloproteinase-7 (MMP7) cleavage of perlecan/HSPG2 creates a molecular switch to alter prostate cancer cell behavior. *Matrix Biol* 2014; 36: 64-76.
- [58] Guglielmi L, Cinnella C, Nardella M, Maresca G, Valentini A, Mercanti D, Felsani A and D'Agnano I. MYCN gene expression is required for the onset of the differentiation programme in neuroblastoma cells. *Cell Death Dis* 2014; 5: e1081.
- [59] McCarthy RC and Kosman DJ. Activation of C6 glioblastoma cell ceruloplasmin expression by neighboring human brain endothelia-derived interleukins in an in vitro blood inverted question mark brain barrier model system. *Cell Commun Signal* 2014; 12: 65.
- [60] Hruz T, Laule O, Szabo G, Wessendorp F, Bleuler S, Oertle L, Widmayer P, Gruissem W and Zimmermann P. Genevestigator v3: a reference expression database for the meta-analysis of transcriptomes. *Adv Bioinformatics* 2008; 2008: 420747.
- [61] Li J, Wang Z, Chong T, Chen H, Li H, Li G, Zhai X and Li Y. Over-expression of a poor prognostic marker in prostate cancer: AQP5 promotes cells growth and local invasion. *World J Surg Oncol* 2014; 12: 284.
- [62] Marchi N, Mazzone P, Fazio V, Mekhail T, Masaryk T and Janigro D. ProApolipoprotein A1: a serum marker of brain metastases in lung cancer patients. *Cancer* 2008; 112: 1313-1324.
- [63] Aguado BA, Wu JJ, Azarin SM, Nanavati D, Rao SS, Bushnell GG, Medicherla CB and Shea LD. Secretome identification of immune cell factors mediating metastatic cell homing. *Sci Rep* 2015; 5: 17566.
- [64] Sung HJ, Ahn JM, Yoon YH, Rhim TY, Park CS, Park JY, Lee SY, Kim JW and Cho JY. Identification and validation of SAA as a potential lung cancer biomarker and its involvement in metastatic pathogenesis of lung cancer. *J Proteome Res* 2011; 10: 1383-1395.
- [65] Knebel FH, Albuquerque RC, Massaro RR, Maria-Engler SS and Campa A. Dual effect of serum amyloid A on the invasiveness of glioma cells. *Mediators Inflamm* 2013; 2013: 509089.
- [66] Mollenhauer J, Wiemann S, Scheurlen W, Korn B, Hayashi Y, Wilgenbus KK, von Deimling A and Poustka A. DMBT1, a new member of the SRCR superfamily, on chromosome 10q25.3-26.1 is deleted in malignant brain tumours. *Nat Genet* 1997; 17: 32-39.

- [67] Muller H, Hu J, Popp R, Schmidt MH, Muller-Decker K, Mollenhauer J, Fisslthaler B, Eble JA and Fleming I. Deleted in malignant brain tumors 1 is present in the vascular extracellular matrix and promotes angiogenesis. *Arterioscler Thromb Vasc Biol* 2012; 32: 442-448.
- [68] Fang ZQ, Zang WD, Chen R, Ye BW, Wang XW, Yi SH, Chen W, He F and Ye G. Gene expression profile and enrichment pathways in different stages of bladder cancer. *Genet Mol Res* 2013; 12: 1479-1489.
- [69] Khalouei S, Chow AM and Brown IR. Stress-induced localization of HSPA6 (HSP70B') and HSPA1A (HSP70-1) proteins to centrioles in human neuronal cells. *Cell Stress Chaperones* 2014; 19: 321-327.
- [70] Adamson DC, Shi Q, Wortham M, Northcott PA, Di C, Duncan CG, Li J, McLendon RE, Bigner DD, Taylor MD and Yan H. OTX2 is critical for the maintenance and progression of classic medulloblastoma. *Cancer Res* 2010; 70: 181-191.
- [71] Yeom SY, Nam DH and Park C. RRAD Promotes EGFR-Mediated STAT3 Activation and Induces Temozolomide Resistance of Malignant Glioblastoma. *Mol Cancer Ther* 2014; 13: 3049-3061.
- [72] Distefano MB, Kjos I, Bakke O and Progida C. Rab7b at the intersection of intracellular trafficking and cell migration. *Commun Integr Biol* 2015; 8: e1023492.
- [73] Iyer A, Zurolo E, Prabowo A, Fluiter K, Spliet WG, van Rijen PC, Gorter JA and Aronica E. MicroRNA-146a: a key regulator of astrocyte-mediated inflammatory response. *PLoS One* 2012; 7: e44789.
- [74] Strickland ER, Hook MA, Balaraman S, Huie JR, Grau JW and Miranda RC. MicroRNA dysregulation following spinal cord contusion: implications for neural plasticity and repair. *Neuroscience* 2011; 186: 146-160.
- [75] Sangar V, Funk CC, Kusebauch U, Campbell DS, Moritz RL and Price ND. Quantitative proteomic analysis reveals effects of epidermal growth factor receptor (EGFR) on invasion-promoting proteins secreted by glioblastoma cells. *Mol Cell Proteomics* 2014; 13: 2618-2631.
- [76] Alam MT, Nagao-Kitamoto H, Ohga N, Akiyama K, Maishi N, Kawamoto T, Shinohara N, Takeuchi A, Shindoh M, Hida Y and Hida K. Suprabasin as a novel tumor endothelial cell marker. *Cancer Sci* 2014; 105: 1533-1540.
- [77] Lee SY, Meier R, Furuta S, Lenburg ME, Kenny PA, Xu R and Bissell MJ. FAM83A confers EGFR-TKI resistance in breast cancer cells and in mice. *J Clin Invest* 2012; 122: 3211-3220.
- [78] Rutkowski MJ, Sughrue ME, Kane AJ, Mills SA and Parsa AT. Cancer and the complement cascade. *Mol Cancer Res* 2010; 8: 1453-1465.
- [79] Kajiwaraya Y, Schiff T, Voloudakis G, Gama Sosa MA, Elder G, Bozdagi O and Buxbaum JD. A critical role for human caspase-4 in endotoxin sensitivity. *J Immunol* 2014; 193: 335-343.
- [80] Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson A, Kampf C, Sjostedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szegedy CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J and Ponten F. Proteomics. Tissue-based map of the human proteome. *Science* 2015; 347: 1260419.
- [81] Huang Y, Prasad M, Lemon WJ, Hampel H, Wright FA, Kornacker K, LiVolsi V, Frankel W, Kloos RT, Eng C, Pellegata NS and de la Chapelle A. Gene expression in papillary thyroid carcinoma reveals highly consistent profiles. *Proc Natl Acad Sci U S A* 2001; 98: 15044-15049.
- [82] Yue X, Zhang Z, Liang X, Gao L, Zhang X, Zhao D, Liu X, Ma H, Guo M, Spear BT, Gong Y and Ma C. Zinc fingers and homeoboxes 2 inhibits hepatocellular carcinoma cell proliferation and represses expression of Cyclins A and E. *Gastroenterology* 2012; 142: 1559-1570, e2.

## Gene expression and biofunctions related to a brain metastasis from a PTC

**Supplement Table 1.** Probe sets differentially expressed in the brain metastatic PTC including its TR vs. non-brain metastatic PTCs and vs. primary brain tumors

| Transcript ID | Gene symbol | Gene name/assignment                                 | Chromosomal location | Brain metastatic PTC + TR vs. non-brain metastatic PTCs |             |             | Brain metastatic PTC + TR vs. primary brain tumors |             |             |
|---------------|-------------|--|----------------------|---|-------------|-------------|--|-------------|-------------|
|               |             |  |                      | p-value   | FDR p-value | Fold change | p-value  | FDR p-value | Fold change |
| 8129134       | ROS1        | ROS proto-oncogene 1, receptor tyrosine kinase       | 6q22                 | 1.93E-14  | 5.61E-10    | 13.37       | 1.17E-14   | 3.40E-10    | 14.70       |
| 7923534       | MYBPH       | myosin binding protein H                             | 1q32.1               | 1.15E-11  | 1.54E-07    | 12.96       | 1.30E-11   | 1.23E-07    | 12.67       |
| 8180303       | --          | --   | 11p15.1              | 2.11E-11  | 2.04E-07    | 75.90       | 2.65E-11   | 1.72E-07    | 70.76       |
| 7927502       | SLC18A3     | solute carrier family 18 member A3                   | 10q11.23             | 1.67E-10  | 1.05E-06    | 11.46       | 1.96E-10   | 8.73E-07    | 11.10       |
| 7997188       | HP          | haptoglobin  | 16q22.2              | 2.58E-10  | 1.48E-06    | 87.76       | 6.72E-10   | 1.75E-06    | 64.41       |
| 7946977       | SAA2-SAA4   | SAA2-SAA4 readthrough                                | 11p15.1              | 3.70E-10  | 1.71E-06    | 5.68        | 2.86E-10   | 1.05E-06    | 5.87        |
| 8091385       | CP          | ceruloplasmin (ferroxidase)                          | 3q24q25.1            | 4.65E-10  | 1.93E-06    | 37.57       | 2.89E-10   | 1.05E-06    | 42.79       |
| 8048864       | CCL20       | chemokine (C-C motif) ligand 20                      | 2q36.3               | 2.53E-09  | 8.58E-06    | 121.78      | 1.48E-09   | 3.04E-06    | 148.82      |
| 8016128       | GFAP        | glial fibrillary acidic protein                      | 17q21                | 2.95E-09  | 8.80E-06    | 3.08        | 1.37E-08   | 1.46E-05    | 2.75        |
| 7904953       | RNU1-120P   | RNA, U1 small nuclear 120, pseudogene                | 1q21.2               | 7.32E-09  | 1.87E-05    | 15.20       | 3.68E-08   | 3.38E-05    | 11.01       |
| 7931108       | DMBT1       | deleted in malignant brain tumors 1                  | 10q26.13             | 7.61E-09  | 1.94E-05    | 3.45        | 1.63E-09   | 3.17E-06    | 4.04        |
| 8051322       | XDH         | xanthine dehydrogenase                               | 2p23.1               | 1.06E-08  | 2.37E-05    | 8.67        | 4.80E-09   | 7.11E-06    | 9.93        |
| 8164464       | ZER1        | zyg-11 related, cell cycle regulator                 | 9q34.11              | 2.09E-08  | 3.69E-05    | -2.88       | 1.21E-07   | 7.44E-05    | -2.52       |
| 8062927       | PI3         | peptidase inhibitor 3, skin-derived                  | 20q13.12             | 2.00E-08  | 3.70E-05    | 4.12        | 1.62E-07   | 9.20E-05    | 3.32        |
| 8095697       | CXCL1       | C-X-C motif chemokine ligand 1                       | 4q13.3               | 1.90E-08  | 3.70E-05    | 11.61       | 5.08E-08   | 4.11E-05    | 9.68        |
| 8038556       | NAPSA       | napsin A aspartic peptidase                          | 19q13.33             | 2.01E-08  | 3.72E-05    | 11.16       | 4.79E-08   | 3.81E-05    | 9.53        |
| 7946983       | SAA2        | serum amyloid A2                                     | 11p15.1              | 3.18E-08  | 4.87E-05    | 6.70        | 1.55E-08   | 1.70E-05    | 7.49        |
| 8103466       | FSTL5       | folliculin-like 5                                    | 4q32.3               | 6.26E-08  | 9.45E-05    | 3.91        | 2.63E-08   | 2.36E-05    | 4.31        |
| 7971950       | DACH1       | dachshund family transcription factor 1              | 13q22                | 9.45E-08  | 1.25E-04    | 3.82        | 8.17E-08   | 5.55E-05    | 3.87        |
| 8109039       | SPINK14     | serine peptidase inhibitor, Kazal type 14 (putative) | 5q32                 | 1.16E-07  | 1.53E-04    | 5.40        | 6.30E-08   | 4.71E-05    | 5.88        |
| 7906764       | HSPA6       | heat shock protein family A (Hsp70) member 6         | 1q23                 | 1.39E-07  | 1.73E-04    | 20.77       | 1.65E-06   | 5.31E-04    | 11.79       |
| 7938758       | SAA1        | serum amyloid A1                                     | 11p15.1              | 1.80E-07  | 1.98E-04    | 7.69        | 1.42E-07   | 7.28E-05    | 7.95        |
| 8044976       | CNTNAP5     | contactin associated protein-like 5                  | 2q14.3               | 2.19E-07  | 2.11E-04    | 4.93        | 2.24E-07   | 1.10E-04    | 4.91        |
| 7979357       | OTX2        | orthodenticle homeobox 2                             | 14q22.3              | 2.07E-07  | 2.16E-04    | 4.66        | 1.28E-07   | 6.95E-05    | 4.92        |
| 7927482       | CHAT        | choline O-acetyltransferase                          | 10q11.2              | 1.89E-07  | 2.18E-04    | 4.96        | 2.46E-07   | 1.25E-04    | 4.79        |
| 8135915       | HILPDA      | hypoxia inducible lipid droplet-associated           | 7q32.1               | 2.26E-07  | 2.44E-04    | 13.83       | 2.57E-07   | 1.28E-04    | 13.47       |
| 8001918       | RRAD        | Ras-related associated with diabetes                 | 16q22                | 2.61E-07  | 2.69E-04    | 15.91       | 2.00E-06   | 6.13E-04    | 10.27       |
| 8056457       | SCN1A       | sodium channel, voltage-gated, type I, alpha subunit | 2q24.3               | 3.02E-07  | 2.94E-04    | 3.72        | 2.14E-07   | 1.07E-04    | 3.87        |
| 8006459       | CCL13       | chemokine (C-C motif) ligand 13                      | 17q11.2              | 4.10E-07  | 3.71E-04    | 8.08        | 3.67E-08   | 3.46E-05    | 12.69       |
| 8061916       | BPIFB9P     | BPI fold containing family B, member 9, pseudogene   | 20q11.21             | 6.03E-07  | 4.85E-04    | 5.56        | 3.31E-07   | 1.47E-04    | 6.06        |
| 8130556       | SOD2        | superoxide dismutase 2, mitochondrial                | 6q25.3               | 5.99E-07  | 5.05E-04    | 7.48        | 1.79E-06   | 5.72E-04    | 6.25        |
| 8010354       | GAA         | glucosidase, alpha; acid                             | 17q25.3              | 8.37E-07  | 6.33E-04    | -3.90       | 1.07E-06   | 3.78E-04    | -3.81       |
| 8015387       | KRT17       | keratin 17   | 17q21.2              | 8.07E-07  | 6.39E-04    | 4.64        | 2.77E-07   | 1.34E-04    | 5.34        |
| 8075316       | OSM         | oncostatin M   | 22q12.2              | 8.33E-07  | 6.64E-04    | 3.43        | 6.68E-06   | 1.48E-03    | 2.80        |
| 8180340       | RAB7B       | RAB7B, member RAS oncogene family                    | 1q32.1               | 1.17E-06  | 8.17E-04    | 3.13        | 3.62E-06   | 8.96E-04    | 2.83        |



## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |           |   |            |          |          |       |          |          |       |
|---------|-----------|---|------------|----------|----------|-------|----------|----------|-------|
| 8109649 | MIR146A   | microRNA 146a   | 5q34       | 1.39E-06 | 9.36E-04 | 3.01  | 8.34E-07 | 2.98E-04 | 3.19  |
| 8030860 | FPR2      | formyl peptide receptor 2                                     | 19q13.41   | 1.45E-06 | 9.78E-04 | 6.86  | 5.19E-06 | 1.24E-03 | 5.61  |
| 8038487 | IL4I1     | interleukin 4 induced 1                                       | 19q13.33   | 1.44E-06 | 9.85E-04 | 2.87  | 5.77E-06 | 1.28E-03 | 2.54  |
| 8095680 | CXCL8     | C-X-C motif chemokine ligand 8                                | 4q13.3     | 1.58E-06 | 1.04E-03 | 39.82 | 8.73E-07 | 3.27E-04 | 48.30 |
| 7912145 | TNFRSF9   | tumor necrosis factor receptor superfamily, member 9          | 1p36       | 1.69E-06 | 1.08E-03 | 3.77  | 3.15E-06 | 8.20E-04 | 3.52  |
| 8070584 | TMPRSS3   | transmembrane protease, serine 3                              | 21q22.3    | 2.13E-06 | 1.33E-03 | 5.95  | 3.19E-07 | 1.46E-04 | 8.04  |
| 8092970 | APOD      | apolipoprotein D  | 3q29       | 2.36E-06 | 1.44E-03 | 24.97 | 1.56E-04 | 1.30E-02 | 8.67  |
| 8043981 | IL1R2     | interleukin 1 receptor, type II                               | 2q12       | 2.97E-06 | 1.79E-03 | 7.74  | 1.18E-05 | 2.08E-03 | 6.12  |
| 7905571 | S100A9    | S100 calcium binding protein A9                               | 1q21       | 3.10E-06 | 1.82E-03 | 8.13  | 3.46E-05 | 4.64E-03 | 5.37  |
| 8036103 | SBSN      | suprabasin  | 19q13.13   | 3.13E-06 | 1.85E-03 | 3.29  | 3.11E-06 | 8.18E-04 | 3.29  |
| 8131803 | IL6       | interleukin 6   | 7p21       | 4.80E-06 | 2.40E-03 | 5.41  | 1.88E-05 | 2.91E-03 | 4.49  |
| 8148184 | FAM83A    | family with sequence similarity 83, member A                  | 8q24.13    | 5.85E-06 | 3.00E-03 | 2.87  | 1.68E-06 | 5.17E-04 | 3.23  |
| 7967318 | HCAR2     | hydroxycarboxylic acid receptor 2                             | 12q24.31   | 6.71E-06 | 3.01E-03 | 2.53  | 7.35E-06 | 1.32E-03 | 2.53  |
| 7967322 | HCAR3     | hydroxycarboxylic acid receptor 3                             | 12q24.31   | 7.42E-06 | 3.30E-03 | 4.23  | 4.39E-06 | 9.46E-04 | 4.53  |
| 7930593 | PLEKHS1   | pleckstrin homology domain containing, family S member 1      | 10q25.3    | 9.04E-06 | 3.79E-03 | 3.33  | 1.20E-05 | 1.95E-03 | 3.23  |
| 7997801 | IL17C     | interleukin 17C   | 16q24      | 9.86E-06 | 4.35E-03 | 2.81  | 2.87E-05 | 3.95E-03 | 2.56  |
| 8100994 | CXCL2     | C-X-C motif chemokine ligand 2                                | 4q21       | 8.94E-06 | 4.38E-03 | 10.63 | 1.01E-06 | 3.65E-04 | 17.55 |
| 8112198 | ACTBL2    | actin, beta-like 2  | 5q11.2     | 9.48E-06 | 4.54E-03 | 9.47  | 1.17E-06 | 4.06E-04 | 14.89 |
| 7906775 | HSPA6     | heat shock protein family A (Hsp70) member 6                  | 1q23       | 9.76E-06 | 4.61E-03 | 8.61  | 4.66E-04 | 2.62E-02 | 4.32  |
| 8162373 | OGN       | osteoglycin   | 9q22       | 1.28E-05 | 5.61E-03 | 26.62 | 5.69E-04 | 3.03E-02 | -9.15 |
| 7965587 | RNU6-247P | RNA, U6 small nuclear 247, pseudogene                         | 12q22q23.1 | 1.30E-05 | 5.74E-03 | 6.64  | 9.69E-06 | 1.85E-03 | 7.00  |
| 8138310 | DGKB      | diacylglycerol kinase, beta 90 kDa                            | 7p21.2     | 1.72E-05 | 6.42E-03 | 4.50  | 3.44E-05 | 4.49E-03 | 4.09  |
| 8038861 | SIGLEC6   | sialic acid binding Ig-like lectin 6                          | 19q13.3    | 1.71E-05 | 7.03E-03 | 30.33 | 7.96E-06 | 1.63E-03 | 38.97 |
| 8054722 | IL1B      | interleukin 1, beta   | 2q14       | 1.69E-05 | 7.10E-03 | 21.10 | 8.06E-04 | 3.69E-02 | 7.63  |
| 8096580 | MTTP      | microsomal triglyceride transfer protein                      | 4q24       | 1.89E-05 | 7.44E-03 | 2.02  | 1.32E-05 | 2.32E-03 | 2.06  |
| 7900146 | ZC3H12A   | zinc finger CCCH-type containing 12A                          | 1p34.3     | 2.52E-05 | 9.60E-03 | 3.10  | 6.55E-06 | 1.42E-03 | 3.58  |
| 8061912 | BPIFB9P   | BPI fold containing family B, member 9, pseudogene            | 20q11.21   | 3.04E-05 | 9.69E-03 | 3.43  | 4.25E-06 | 9.48E-04 | 4.27  |
| 8173174 | USP51     | ubiquitin specific peptidase 51                               | Xp11.21    | 2.59E-05 | 9.72E-03 | -3.09 | 4.85E-05 | 6.04E-03 | -2.89 |
| 7904244 | MAB21L3   | mab-21-like 3 (C. elegans)                                    | 1p13.1     | 3.55E-05 | 1.15E-02 | 3.26  | 1.04E-05 | 1.87E-03 | 3.77  |
| 7951217 | MMP7      | matrix metalloproteinase 7                                    | 11q22.2    | 3.81E-05 | 1.20E-02 | 18.25 | 2.91E-05 | 4.20E-03 | 19.70 |
| 8167887 | MAGEH1    | melanoma antigen family H, 1                                  | Xp11.21    | 3.80E-05 | 1.20E-02 | -4.11 | 4.52E-06 | 1.12E-03 | -5.60 |
| 8104234 | TRIP13    | thyroid hormone receptor interactor 13                        | 5p15.33    | 4.03E-05 | 1.31E-02 | 2.44  | 1.33E-04 | 1.17E-02 | 2.20  |
| 8046815 | ZNF804A   | zinc finger protein 804A                                      | 2q32.1     | 5.48E-05 | 1.35E-02 | 4.11  | 5.38E-04 | 2.53E-02 | 3.09  |
| 8147065 | RALYL     | RALY RNA binding protein-like                                 | 8q21.2     | 4.52E-05 | 1.39E-02 | 2.32  | 2.34E-05 | 3.49E-03 | 2.45  |
| 8156873 | INVS      | inversin  | 9q31       | 4.68E-05 | 1.42E-02 | -2.40 | 6.27E-06 | 1.44E-03 | -2.87 |
| 8033445 | CD209     | CD209 molecule  | 19p13      | 5.27E-05 | 1.45E-02 | 6.53  | 5.49E-05 | 6.13E-03 | 6.47  |
| 7998063 | TUBB3     | tubulin, beta 3 class III                                     | 16q24.3    | 4.80E-05 | 1.49E-02 | 2.30  | 1.45E-04 | 1.25E-02 | 2.11  |
| 8049075 | B3GNT7    | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7 | 2q37.1     | 5.68E-05 | 1.50E-02 | 3.23  | 4.32E-06 | 1.05E-03 | 4.42  |
| 7955297 | AQP5      | aquaporin 5   | 12q13      | 5.08E-05 | 1.52E-02 | 10.24 | 1.26E-05 | 2.23E-03 | 14.28 |
| 7921076 | GPATCH4   | G patch domain containing 4                                   | 1q22       | 6.46E-05 | 1.78E-02 | 2.99  | 2.59E-05 | 3.75E-03 | 3.32  |
| 7981333 | RN7SL472P | RNA, 7SL, cytoplasmic 472, pseudogene                         | 4q32.31    | 6.65E-05 | 1.81E-02 | 21.88 | 1.62E-04 | 1.33E-02 | 16.68 |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |          |   |          |          |          |        |          |          |       |
|---------|----------|---|----------|----------|----------|--------|----------|----------|-------|
| 7908907 | ADORA1   | adenosine A1 receptor                                       | 1q32.1   | 7.42E-05 | 1.94E-02 | 2.93   | 1.70E-07 | 9.50E-05 | 6.35  |
| 7923875 | C1orf186 | chromosome 1 open reading frame 186                         | 1q32.1   | 7.92E-05 | 2.02E-02 | 5.00   | 1.29E-05 | 2.23E-03 | 6.78  |
| 8086961 | PFKFB4   | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4       | 3p21.31  | 9.40E-05 | 2.26E-02 | 2.93   | 7.29E-04 | 3.52E-02 | 2.35  |
| 8155794 | C9orf85  | chromosome 9 open reading frame 85                          | 9q21.13  | 1.40E-04 | 2.36E-02 | -3.64  | 4.94E-05 | 5.12E-03 | -4.11 |
| 7992828 | IL32     | interleukin 32  | 16p13.3  | 1.16E-04 | 2.39E-02 | 4.31   | 7.26E-04 | 3.20E-02 | 3.32  |
| 8119403 | APOBEC2  | apolipoprotein B mRNA editing enzyme catalytic subunit 2    | 6p21.1   | 1.57E-04 | 2.54E-02 | 3.77   | 1.67E-05 | 2.41E-03 | 4.95  |
| 8156581 | ERCC6L2  | excision repair cross-complementation group 6-like 2        | 9q22.32  | 1.20E-04 | 2.62E-02 | -2.33  | 2.84E-04 | 1.92E-02 | -2.17 |
| 8110841 | LPCAT1   | lysophosphatidylcholine acyltransferase 1                   | 5p15.33  | 1.40E-04 | 2.84E-02 | 3.19   | 7.45E-05 | 8.10E-03 | 3.45  |
| 8168749 | SRPX2    | sushi-repeat containing protein, X-linked 2                 | Xq22.1   | 1.46E-04 | 2.91E-02 | 4.47   | 5.03E-06 | 1.22E-03 | 7.93  |
| 7943413 | BIRC3    | baculoviral IAP repeat containing 3                         | 11q22    | 1.64E-04 | 2.97E-02 | 16.36  | 4.68E-05 | 5.65E-03 | 23.77 |
| 7909371 | CR1      | complement component 3b/4b receptor 1 (Knops blood group)   | 1q32.2   | 1.67E-04 | 3.11E-02 | 3.34   | 7.19E-04 | 3.38E-02 | 2.78  |
| 8169504 | SLC6A14  | solute carrier family 6 (amino acid transporter), member 14 | Xq23     | 1.75E-04 | 3.13E-02 | 15.62  | 1.30E-05 | 2.23E-03 | 33.84 |
| 7983478 | C15orf48 | chromosome 15 open reading frame 48                         | 15q21.1  | 1.71E-04 | 3.23E-02 | 6.27   | 1.92E-05 | 3.01E-03 | 9.84  |
| 8016033 | FAM171A2 | family with sequence similarity 171, member A2              | 17q21.31 | 1.93E-04 | 3.40E-02 | -3.63  | 1.18E-04 | 1.08E-02 | -3.89 |
| 8006865 | PPP1R1B  | protein phosphatase 1, regulatory (inhibitor) subunit 1B    | 17q12    | 2.33E-04 | 3.87E-02 | 4.06   | 2.91E-04 | 1.94E-02 | 3.92  |
| 8126248 | UNC5CL   | unc-5 homolog C (C. elegans)-like                           | 6p21.1   | 2.48E-04 | 3.96E-02 | 5.01   | 1.87E-05 | 2.97E-03 | 8.06  |
| 8104901 | IL7R     | interleukin 7 receptor                                      | 5p13     | 2.88E-04 | 4.38E-02 | 9.07   | 9.49E-04 | 4.08E-02 | 6.81  |
| 7923347 | LAD1     | ladinin 1   | 1q32.1   | 3.19E-04 | 4.65E-02 | 3.49   | 5.01E-08 | 4.24E-05 | 16.03 |
| 8158725 | ABL1     | ABL proto-oncogene 1, non-receptor tyrosine kinase          | 9q34.1   | 3.16E-04 | 4.66E-02 | -2.71  | 1.28E-04 | 1.17E-02 | -3.01 |
| 8083233 | ZIC1     | Zic family member 1   | 3q24     | 6.98E-06 |          | 17.37  | 3.07E-02 |          | -2.69 |
| 8072678 | HMOX1    | heme oxygenase (decycling) 1                                | 22q13.1  | 4.33E-05 |          | 4.92   | 2.11E-03 |          | 2.79  |
| 8099476 | PROM1    | prominin 1  | 4p15.32  | 1.17E-04 |          | 16.06  | 1.73E-03 |          | 7.62  |
| 7988350 | DUOX2    | dual oxidase 2  | 15q15.3  | 1.32E-04 |          | -19.36 | 4.31E-02 |          | 3.55  |
| 7953603 | C1S      | complement component 1, s subcomponent                      | 12p13    | 1.58E-04 |          | 13.15  | 1.70E-02 |          | -3.98 |
| 8122701 | -        | -   | 6q25.1   | 1.65E-04 |          | -5.66  | 2.95E-03 |          | -3.43 |
| 8102342 | ELOVL6   | ELOVL fatty acid elongase 6                                 | 4q25     | 1.66E-04 |          | 7.20   | 1.15E-02 |          | 3.09  |
| 8054712 | IL1A     | interleukin 1, alpha  | 2q14     | 1.68E-04 |          | 8.26   | 1.67E-02 |          | 3.09  |
| 8156633 | CCDC180  | coiled-coil domain containing 180                           | 9q22.33  | 1.76E-04 |          | -2.72  | 1.10E-03 |          | -2.25 |
| 8157446 | ORM1     | orosomucoid 1   | 9q32     | 1.98E-04 |          | 4.95   | 3.07E-05 |          | 6.43  |
| 7940441 | PGA3     | pepsinogen 3, group I (pepsinogen A)                        | 11q12.2  | 2.67E-04 |          | 3.77   | 9.14E-04 |          | 3.19  |
| 8157700 | RABGAP1  | RAB GTPase activating protein 1                             | 9q34.11  | 2.85E-04 |          | -2.84  | 2.51E-03 |          | -2.23 |
| 8111220 | CDH18    | cadherin 18, type 2   | 5p14.3   | 3.02E-04 |          | 2.17   | 2.58E-04 |          | 2.22  |
| 7940177 | OR4D10   | olfactory receptor, family 4, subfamily D, member 10        | 11q12    | 3.19E-04 |          | 7.26   | 8.51E-05 |          | 9.74  |
| 8034837 | DNAJB1   | DnaJ (Hsp40) homolog, subfamily B, member 1                 | 19p13.2  | 3.20E-04 |          | 4.41   | 3.91E-03 |          | 2.96  |
| 8147469 | CPQ      | carboxypeptidase Q  | 8q22.2   | 3.28E-04 |          | -3.12  | 2.58E-04 |          | -3.23 |
| 8094743 | RHOH     | ras homolog family member H                                 | 4p13     | 3.42E-04 |          | 3.23   | 1.18E-02 |          | 2.06  |
| 8156601 | ERCC6L2  | excision repair cross-complementation group 6-like 2        | 9q22.32  | 3.53E-04 |          | -2.58  | 1.96E-03 |          | -2.15 |
| 8130580 | SNORA29  | small nucleolar RNA, H/ACA box 29                           | 6q25.3   | 3.69E-04 |          | 3.17   | 3.84E-04 |          | 3.15  |
| 8140151 | RFC2     | replication factor C (activator 1) 2, 40 kDa                | 7q11.23  | 3.75E-04 |          | 2.12   | 1.08E-05 |          | 2.91  |
| 8147461 | SDC2     | syndecan 2  | 8q22.1   | 3.88E-04 |          | -2.43  | 1.07E-04 |          | -2.77 |
| 8132960 | SNORA22  | Small nucleolar RNA SNORA22                                 | 7p11.2   | 3.89E-04 |          | 2.69   | 1.62E-03 |          | 2.30  |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |           |   |          |          |       |          |        |
|---------|-----------|---|----------|----------|-------|----------|--------|
| 8109677 | GABRG2    | gamma-aminobutyric acid (GABA) A receptor, gamma 2      | 5q34     | 4.11E-04 | 2.43  | 1.55E-04 | 2.67   |
| 8115584 | CCNJL     | cyclin J-like   | 5q33.3   | 4.53E-04 | 3.12  | 1.27E-05 | 5.06   |
| 8180246 | --        | --  | --       | 4.73E-04 | -5.54 | 5.84E-03 | -3.53  |
| 7940431 | PGA3      | pepsinogen 3, group I (pepsinogen A)                    | 11q12.2  | 5.30E-04 | 3.86  | 1.92E-03 | 3.20   |
| 8138566 | IGF2BP3   | insulin-like growth factor 2 mRNA binding protein 3     | 7p11     | 5.35E-04 | 3.34  | 9.50E-05 | 4.30   |
| 7909164 | CTSE      | cathepsin E   | 1q31     | 5.69E-04 | 92.12 | 2.17E-04 | 155.04 |
| 7952339 | SNORD14C  | small nucleolar RNA, C/D box 14C                        | 11q24.1  | 5.93E-04 | 9.74  | 4.51E-02 | 3.11   |
| 8106168 | --        | Y_RNA ENSG00000200833                                   | 5q13.2   | 5.94E-04 | 2.51  | 5.69E-04 | 2.52   |
| 7944751 | C11orf63  | chromosome 11 open reading frame 63                     | 11q24.1  | 6.01E-04 | -3.32 | 6.34E-05 | -4.61  |
| 7983910 | AQP9      | aquaporin 9   | 15q      | 6.02E-04 | 13.61 | 1.14E-03 | 11.19  |
| 7990818 | BCL2A1    | BCL2-related protein A1                                 | 15q24.3  | 6.13E-04 | 4.28  | 9.18E-04 | 4.00   |
| 7908639 | C1orf106  | chromosome 1 open reading frame 106                     | 1q32.1   | 6.54E-04 | 2.49  | 4.25E-04 | 2.61   |
| 8032509 | GNG7      | guanine nucleotide binding protein (G protein), gamma 7 | 19p13.3  | 6.83E-04 | -2.28 | 2.01E-07 | -5.66  |
| 7940421 | PGA3      | pepsinogen 3, group I (pepsinogen A)                    | 11q12.2  | 6.96E-04 | 3.67  | 2.50E-03 | 3.04   |
| 7905533 | IVL       | involucrin  | 1q21     | 7.00E-04 | 2.73  | 4.57E-04 | 2.88   |
| 8124534 | HIST1H4L  | histone cluster 1, H4I                                  | 6p22.1   | 7.22E-04 | 3.27  | 4.98E-03 | 2.50   |
| 7924508 | SUSD4     | sushi domain containing 4                               | 1q41     | 7.33E-04 | 3.19  | 2.38E-05 | 5.16   |
| 8118310 | HSPA1A    | heat shock 70 kDa protein 1A                            | 6p21.3   | 7.39E-04 | 6.05  | 9.50E-03 | 3.52   |
| 8025402 | ANGPTL4   | angiopoietin-like 4                                     | 19p13.3  | 7.58E-04 | 11.86 | 6.51E-05 | 25.38  |
| 8179322 | HSPA1A    | heat shock 70 kDa protein 1A                            | 6p21.3   | 7.71E-04 | 6.09  | 9.60E-03 | 3.55   |
| 8123864 | TFAP2A    | transcription factor AP-2 alpha                         | 6p24.3   | 7.76E-04 | 3.36  | 5.67E-03 | 2.53   |
| 8157027 | NIPSNAP3B | nipsnap homolog 3B (C. elegans)                         | 9q31.1   | 8.39E-04 | -3.03 | 2.86E-03 | -2.57  |
| 7951928 | DSCAML1   | Down syndrome cell adhesion molecule like 1             | 11q23    | 8.51E-04 | 2.72  | 5.55E-04 | 2.83   |
| 7907861 | XPR1      | xenotropic and polytropic retrovirus receptor 1         | 1q25.1   | 8.52E-04 | 3.02  | 2.79E-06 | 7.13   |
| 7969640 | CLDN10    | claudin 10  | 13q32.1  | 9.46E-04 | 6.07  | 9.87E-05 | 10.21  |
| 8026272 | IL27RA    | interleukin 27 receptor, alpha                          | 19p13.11 | 1.01E-03 | 3.65  | 5.75E-04 | 3.99   |
| 8162388 | OMD       | osteomodulin  | 9q22.31  | 1.03E-03 | 7.74  | 1.55E-05 | -22.52 |
| 8104449 | CCT5      | chaperonin containing TCP1, subunit 5 (epsilon)         | 5p15.2   | 1.04E-03 | 2.50  | 4.41E-03 | 2.13   |
| 7928602 | SFTPA1    | surfactant protein A1                                   | 10q22.3  | 1.05E-03 | 30.04 | 1.42E-04 | 71.83  |
| 7928632 | SFTPA1    | surfactant protein A1                                   | 10q22.3  | 1.05E-03 | 30.04 | 1.42E-04 | 71.83  |
| 8097116 | RNU4-33P  | RNA, U4 small nuclear 33, pseudogene                    | ---      | 1.08E-03 | 2.44  | 6.65E-04 | 2.58   |
| 8109639 | PTTG1     | pituitary tumor-transforming 1                          | 5q35.1   | 1.10E-03 | 3.70  | 3.55E-06 | 9.46   |
| 8156604 | ERCC6L2   | excision repair cross-complementation group 6-like 2    | 9q22.32  | 1.10E-03 | -2.26 | 8.46E-04 | -2.32  |
| 7915472 | SLC2A1    | solute carrier family 2 member 1                        | 1p34.2   | 1.12E-03 | 4.81  | 6.13E-04 | 5.41   |
| 7975987 | SNORA46   | small nucleolar RNA, H/ACA box 46                       | 14q24.3  | 1.12E-03 | 3.24  | 3.53E-03 | 2.75   |
| 7922756 | NMNAT2    | nicotinamide nucleotide adenyltransferase 2             | 1q25     | 1.13E-03 | 6.39  | 4.52E-02 | -2.72  |
| 7909681 | PROX1     | prospero homeobox 1                                     | 1q41     | 1.14E-03 | 4.00  | 1.30E-05 | 9.30   |
| 8124848 | IER3      | immediate early response 3                              | 6p21.3   | 1.15E-03 | 4.55  | 2.15E-03 | 4.06   |
| 8179704 | IER3      | immediate early response 3                              | 6p21.3   | 1.15E-03 | 4.55  | 2.15E-03 | 4.06   |
| 8106141 | FCHO2     | FCH domain only 2                                       | 5q13.2   | 1.18E-03 | 2.42  | 5.41E-05 | 3.44   |
| 7934698 | SFTPA2    | surfactant protein A2                                   | 10q22.3  | 1.19E-03 | 28.20 | 1.84E-04 | 63.22  |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |          |  |               |          |       |          |        |
|---------|----------|--|---------------|----------|-------|----------|--------|
| 7934708 | SFTP2    | surfactant protein A2  | 10q22.3       | 1.19E-03 | 28.20 | 1.84E-04 | 63.22  |
| 7920244 | S100A8   | S100 calcium binding protein A8                                      | 1q21          | 1.23E-03 | 15.82 | 1.97E-02 | 6.11   |
| 7993638 | TMC5     | transmembrane channel-like 5   | 16p12.3       | 1.27E-03 | 3.33  | 2.25E-04 | 4.09   |
| 7996022 | CCL22    | chemokine (C-C motif) ligand 22                                      | 16q13         | 1.31E-03 | 2.62  | 9.32E-04 | 2.73   |
| 7977046 | TNFAIP2  | tumor necrosis factor, alpha-induced protein 2                       | 14q32         | 1.36E-03 | 7.55  | 2.45E-03 | 6.49   |
| 8046408 | PDK1     | pyruvate dehydrogenase kinase, isozyme 1                             | 2q31.1        | 1.37E-03 | 3.42  | 1.46E-03 | 3.38   |
| 8029465 | BCL3     | B-cell CLL/lymphoma 3  | 19q13.32      | 1.37E-03 | 3.64  | 3.09E-04 | 4.55   |
| 8157038 | SLC44A1  | solute carrier family 44 (choline transporter), member 1             | 9q31.1        | 1.43E-03 | -3.33 | 1.77E-02 | -2.26  |
| 7952335 | SNORD14E | small nucleolar RNA, C/D box 14E                                     | 11q24.1       | 1.48E-03 | 13.41 | 8.05E-03 | 7.63   |
| 7909441 | G0S2     | G0/G1 switch 2   | 1q32.2        | 1.52E-03 | 6.18  | 5.85E-04 | 7.74   |
| 8118314 | HSPA1B   | heat shock 70 kDa protein 1B   | 6p21.3        | 1.54E-03 | 6.11  | 9.28E-03 | 4.02   |
| 8178435 | IER3     | immediate early response 3   | 6p21.3        | 1.63E-03 | 4.61  | 2.12E-03 | 4.38   |
| 8090433 | MGLL     | monoglyceride lipase   | 3q21.3        | 1.63E-03 | 4.32  | 8.08E-03 | 3.19   |
| 8156743 | FOXE1    | forkhead box E1 (thyroid transcription factor 2)                     | 9q22          | 1.64E-03 | -3.74 | 3.10E-04 | 4.98   |
| 8178086 | HSPA1B   | heat shock 70 kDa protein 1B   | 6p21.3        | 1.66E-03 | 6.10  | 9.98E-03 | 4.00   |
| 8179324 | HSPA1B   | heat shock 70 kDa protein 1B   | 6p21.3        | 1.66E-03 | 6.10  | 9.98E-03 | 4.00   |
| 8114249 | CXCL14   | chemokine (C-X-C motif) ligand 14                                    | 5q31          | 1.67E-03 | 52.97 | 3.70E-04 | 117.45 |
| 8098637 | CYP4V2   | cytochrome P450, family 4, subfamily V, polypeptide 2                | 4q35.2        | 1.75E-03 | -2.67 | 5.51E-03 | -2.29  |
| 7988426 | SLC30A4  | solute carrier family 30 (zinc transporter), member 4                | 15q21.1       | 1.81E-03 | -2.66 | 8.77E-04 | -2.92  |
| 8075886 | IL2RB    | interleukin 2 receptor, beta   | 22q13.1       | 1.82E-03 | 3.91  | 3.74E-03 | 3.46   |
| 8140504 | MAGI2    | membrane associated guanylate kinase, WW and PDZ domain containing 2 | 7q21.11       | 1.83E-03 | -3.01 | 1.27E-04 | -4.51  |
| 8065344 | FOXA2    | forkhead box A2  | 20p11         | 1.88E-03 | 2.55  | 7.04E-04 | 2.89   |
| 7937079 | BNIP3    | BCL2/adenovirus E1B 19 kDa interacting protein 3                     | -             | 1.91E-03 | 2.74  | 4.12E-06 | 6.68   |
| 7976698 | EML1     | echinoderm microtubule associated protein like 1                     | 14q32         | 1.93E-03 | -4.17 | 2.49E-03 | -3.97  |
| 8103894 | ENPP6    | ectonucleotide pyrophosphatase/phosphodiesterase 6                   | 4q35.1        | 1.95E-03 | 3.04  | 3.67E-09 | -43.97 |
| 8126820 | GPR110   | G protein-coupled receptor 110                                       | 6p12.3        | 2.23E-03 | 6.42  | 1.30E-06 | 54.13  |
| 8080847 | C3orf14  | chromosome 3 open reading frame 14                                   | 3p14.2        | 2.29E-03 | -3.02 | 2.50E-04 | -4.11  |
| 8037374 | PLAUR    | plasminogen activator, urokinase receptor                            | 19q13         | 2.32E-03 | 3.87  | 1.47E-02 | 2.77   |
| 7923850 | SLC26A9  | solute carrier family 26 (anion exchanger), member 9                 | 1q32.1        | 2.35E-03 | 12.40 | 3.87E-04 | 23.32  |
| 8139433 | MYO1G    | myosin IG  | 7p13          | 2.49E-03 | 25.19 | 5.86E-04 | 48.18  |
| 8167027 | RGN      | regucalcin   | Xp11.3        | 2.60E-03 | -2.89 | 3.72E-04 | 3.77   |
| 8155930 | GCNT1    | glucosaminyl (N-acetyl) transferase 1, core 2                        | 9q13          | 2.62E-03 | -4.66 | 3.14E-02 | 2.73   |
| 7925589 | SMYD3    | SET and MYND domain containing 3                                     | 1q44          | 2.63E-03 | 3.81  | 6.28E-05 | 7.63   |
| 8130645 | PARK2    | parkin RBR E3 ubiquitin protein ligase                               | 6q26          | 2.70E-03 | -2.34 | 1.17E-04 | -3.43  |
| 7918533 | ADORA3   | adenosine A3 receptor  | 1p13.2        | 2.72E-03 | 3.75  | 4.21E-02 | -2.26  |
| 8104307 | C5orf38  | chromosome 5 open reading frame 38                                   | 5p15.33       | 2.91E-03 | 5.03  | 2.92E-03 | 5.03   |
| 8106923 | NR2F1    | nuclear receptor subfamily 2, group F, member 1                      | 5q14          | 2.97E-03 | 2.88  | 1.69E-03 | -3.13  |
| 8162059 | SLC28A3  | solute carrier family 28 (concentrative nucleoside transport         | 9q21.32q21.33 | 3.08E-03 | 3.68  | 3.12E-04 | 5.55   |
| 8163795 | PSMD5    | proteasome (prosome, macropain) 26S subunit, non-ATPase, 5           | 9q33.2        | 3.12E-03 | -3.66 | 1.65E-03 | -4.11  |
| 7930921 | BAG3     | BCL2-associated athanogene 3   | 10q26.11      | 3.33E-03 | 2.39  | 8.90E-04 | 2.81   |
| 8087739 | CISH     | cytokine inducible SH2-containing protein                            | 3p21.3        | 3.49E-03 | 2.50  | 1.62E-06 | 7.76   |



## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |            |   |          |          |       |          |        |
|---------|------------|---|----------|----------|-------|----------|--------|
| 7933084 | NAMPT      | nicotinamide phosphoribosyltransferase                | 7q22.3   | 3.59E-03 | 4.88  | 2.50E-02 | 3.12   |
| 8144488 | LINC00965  | long intergenic non-protein coding RNA 965            | 8p23.1   | 3.62E-03 | -2.72 | 2.41E-03 | -2.88  |
| 8070467 | TMPRSS2    | transmembrane protease, serine 2                      | 21q22.3  | 3.63E-03 | 10.95 | 1.60E-04 | 33.23  |
| 8065607 | PLAGL2     | pleiomorphic adenoma gene-like 2                      | 20q11.21 | 3.65E-03 | 2.24  | 7.92E-04 | 2.67   |
| 8142120 | NAMPT      | nicotinamide phosphoribosyltransferase                | 7q22.3   | 3.74E-03 | 4.79  | 3.48E-02 | 2.87   |
| 8161418 | -          | -   | -        | 3.81E-03 | 3.53  | 1.41E-04 | 6.54   |
| 8051133 | FTH1P3     | ferritin, heavy polypeptide 1 pseudogene 3            | 2p23.3   | 3.95E-03 | 2.46  | 5.43E-03 | 2.36   |
| 8062395 | NNAT       | neuronatin  | 20q11.23 | 3.97E-03 | 60.79 | 1.81E-02 | 24.33  |
| 8064939 | TMX4       | thioredoxin-related transmembrane protein 4           | 20p12    | 4.10E-03 | -2.96 | 1.52E-02 | -2.41  |
| 8009443 | ARSG       | arylsulfatase G                                       | 17q24.2  | 4.27E-03 | -2.47 | 3.22E-03 | -2.57  |
| 7912638 | TMEM51-AS1 | TMEM51 antisense RNA 1                                | 1p36.21  | 4.33E-03 | 2.42  | 6.91E-03 | 2.28   |
| 8099834 | TLR1       | toll-like receptor 1                                  | 4p14     | 4.59E-03 | 2.74  | 3.67E-03 | -2.80  |
| 7968212 | WASF3      | WAS protein family, member 3                          | 13q12    | 4.62E-03 | -3.40 | 1.10E-04 | -6.85  |
| 8120552 | FAM135A    | family with sequence similarity 135, member A         | 6q13     | 4.70E-03 | -2.54 | 7.31E-04 | -3.30  |
| 8144410 | LINC00965  | long intergenic non-protein coding RNA 965            | 8p23.1   | 4.72E-03 | -3.50 | 5.77E-03 | -3.37  |
| 7940175 | OR4D6      | olfactory receptor, family 4, subfamily D, member 6   | 11q12.1  | 4.76E-03 | 5.40  | 1.48E-03 | 7.22   |
| 7908924 | PRELP      | proline/arginine-rich end leucine-rich repeat protein | 1q32.1   | 4.84E-03 | 4.24  | 4.23E-03 | -4.33  |
| 7919028 | TBX15      | T-box 15  | 1p11.1   | 4.86E-03 | 3.25  | 2.91E-05 | -8.42  |
| 7978544 | EGLN3      | egl-9 family hypoxia-inducible factor 3               | 14q13.1  | 4.92E-03 | 3.77  | 1.08E-02 | 3.25   |
| 8086185 | PLCD1      | phospholipase C, delta 1                              | 3p22.2   | 4.92E-03 | -2.73 | 1.39E-03 | -3.31  |
| 7953735 | LINC00965  | long intergenic non-protein coding RNA 965            | 8p23.1   | 5.11E-03 | -3.16 | 7.00E-03 | -2.99  |
| 8032834 | LRG1       | leucine-rich alpha-2-glycoprotein 1                   | 19p13.3  | 5.11E-03 | 2.30  | 8.89E-04 | 2.78   |
| 7938777 | LDHA       | lactate dehydrogenase A                               | 11p15.4  | 5.11E-03 | 3.14  | 3.87E-02 | 2.20   |
| 8043441 | IGKV1D-27  | immunoglobulin kappa variable 1D-27 (pseudogene)      | 2p11.2   | 5.14E-03 | 4.29  | 6.82E-03 | 4.05   |
| 7907171 | BLZF1      | basic leucine zipper nuclear factor 1                 | 1q24     | 5.22E-03 | 2.13  | 2.30E-03 | 2.34   |
| 7903959 | PIFO       | primary cilia formation                               | 1p13.2   | 5.36E-03 | -2.72 | 1.99E-02 | 2.23   |
| 7922976 | PTGS2      | prostaglandin-endoperoxide synthase 2                 | 1q31.1   | 5.41E-03 | 10.38 | 1.24E-03 | 17.62  |
| 8025601 | ICAM1      | intercellular adhesion molecule 1                     | 19p13.2  | 5.48E-03 | 5.44  | 2.60E-04 | 12.12  |
| 8116983 | CD83       | CD83 molecule   | 6p23     | 5.52E-03 | 3.03  | 1.76E-03 | 3.66   |
| 8025382 | CERS4      | ceramide synthase 4                                   | 19p13.2  | 5.73E-03 | -2.38 | 1.09E-02 | 2.18   |
| 8006433 | CCL2       | chemokine (C-C motif) ligand 2                        | 17q12    | 5.86E-03 | 12.01 | 1.38E-02 | 8.64   |
| 7937852 | SLC22A18   | solute carrier family 22, member 18                   | 11p15.5  | 5.87E-03 | 2.10  | 2.47E-03 | 2.32   |
| 8162610 | CDC14B     | cell division cycle 14B                               | 9q22.3   | 5.94E-03 | -3.16 | 7.52E-03 | -3.03  |
| 7922243 | METTL18    | methyltransferase like 18                             | 1q24.2   | 6.04E-03 | 3.21  | 6.56E-04 | 4.81   |
| 7931930 | PRKCQ      | protein kinase C, theta                               | 10p15    | 6.07E-03 | -2.21 | 5.40E-05 | 4.06   |
| 7931914 | IL2RA      | interleukin 2 receptor, alpha                         | 10p15.1  | 6.08E-03 | 4.26  | 2.50E-02 | 3.09   |
| 7967544 | SCARB1     | scavenger receptor class B, member 1                  | 12q24.31 | 6.24E-03 | -2.50 | 8.25E-04 | -3.35  |
| 7984588 | THSD4      | thrombospondin, type I, domain containing 4           | 15q23    | 6.28E-03 | -2.39 | 9.22E-09 | -25.45 |
| 8054580 | BUB1       | BUB1 mitotic checkpoint serine/threonine kinase       | 2q13     | 6.34E-03 | 4.47  | 5.12E-04 | 8.13   |
| 8006594 | CCL18      | C-C motif chemokine ligand 18                         | 17q12    | 6.43E-03 | 14.96 | 1.92E-04 | 68.79  |
| 8144416 | LINC00965  | long intergenic non-protein coding RNA 965            | 8p23.1   | 6.48E-03 | -3.60 | 8.52E-03 | -3.40  |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |           |  |         |          |       |          |       |
|---------|-----------|--|---------|----------|-------|----------|-------|
| 8144418 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 6.48E-03 | -3.60 | 8.52E-03 | -3.40 |
| 8144490 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 6.48E-03 | -3.60 | 8.52E-03 | -3.40 |
| 8144492 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 6.48E-03 | -3.60 | 8.52E-03 | -3.40 |
| 8148501 | PTP4A3    | protein tyrosine phosphatase type IVA, member 3                | 8q24.3  | 6.59E-03 | 4.15  | 2.38E-04 | 8.82  |
| 7909214 | RASSF5    | Ras association domain family member 5                         | 1q32.1  | 6.66E-03 | 3.05  | 3.26E-03 | 3.45  |
| 7946401 | ST5       | suppression of tumorigenicity 5                                | 11p15   | 6.68E-03 | 2.76  | 9.50E-03 | 2.62  |
| 8098423 | NEIL3     | nei endonuclease VIII-like 3 (E. coli)                         | 4q34.3  | 6.93E-03 | 2.83  | 3.99E-03 | 3.10  |
| 8042144 | REL       | v-rel avian reticuloendotheliosis viral oncogene homolog       | 2p13    | 6.96E-03 | 2.99  | 1.12E-03 | 4.12  |
| 8111772 | DAB2      | Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila) | 5p13.1  | 7.05E-03 | 3.89  | 3.54E-02 | -2.73 |
| 8149218 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.11E-03 | -3.59 | 9.38E-03 | -3.39 |
| 8149220 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.11E-03 | -3.59 | 9.38E-03 | -3.39 |
| 8149222 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.11E-03 | -3.59 | 9.38E-03 | -3.39 |
| 8149224 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.11E-03 | -3.59 | 9.38E-03 | -3.39 |
| 8149226 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.11E-03 | -3.59 | 9.38E-03 | -3.39 |
| 8157300 | BSPRY     | B-box and SPRY domain containing                               | 9q32    | 7.20E-03 | -2.28 | 9.58E-04 | 2.98  |
| 8141076 | PON2      | paraoxonase 2  | 7q21.3  | 7.29E-03 | 2.62  | 1.30E-02 | 2.41  |
| 8099541 | QDPR      | quinoid dihydropteridine reductase                             | 4p15.31 | 7.30E-03 | -3.34 | 1.33E-02 | -3.00 |
| 8149161 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.31E-03 | -3.30 | 7.36E-03 | -3.29 |
| 8149210 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.31E-03 | -3.30 | 7.36E-03 | -3.29 |
| 8149228 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.37E-03 | -3.14 | 1.11E-02 | -2.92 |
| 8088979 | VGLL3     | vestigial-like family member 3                                 | 3p12.1  | 7.51E-03 | 2.31  | 3.71E-03 | 2.55  |
| 8043697 | ANKRD36B  | ankyrin repeat domain 36B                                      | 2q11.2  | 7.52E-03 | -3.05 | 2.11E-02 | -2.56 |
| 8161964 | FRMD3     | FERM domain containing 3                                       | 9q21.32 | 7.57E-03 | -3.99 | 3.35E-03 | 4.87  |
| 8167728 | SSX2B     | synovial sarcoma, X breakpoint 2B                              | Xp11.22 | 7.64E-03 | 2.75  | 5.52E-05 | 6.04  |
| 8149216 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.76E-03 | -3.48 | 1.01E-02 | -3.29 |
| 8144420 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.78E-03 | -3.38 | 7.03E-03 | -3.45 |
| 8144494 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.78E-03 | -3.38 | 7.03E-03 | -3.45 |
| 8149151 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.80E-03 | -3.35 | 8.85E-03 | -3.26 |
| 8149214 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.80E-03 | -3.35 | 8.85E-03 | -3.26 |
| 8149153 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.88E-03 | -3.34 | 7.65E-03 | -3.35 |
| 8149157 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.88E-03 | -3.34 | 7.65E-03 | -3.35 |
| 8144412 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.88E-03 | -3.20 | 1.04E-02 | -3.04 |
| 8144414 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 7.88E-03 | -3.20 | 1.04E-02 | -3.04 |
| 7948229 | SLC43A3   | solute carrier family 43, member 3                             | 11q11   | 7.88E-03 | 6.63  | 6.48E-03 | 7.05  |
| 8095819 | FAM47E    | family with sequence similarity 47, member E                   | 4q21.1  | 7.88E-03 | -2.67 | 1.27E-03 | 3.55  |
| 7980485 | DIO2      | deiodinase, iodothyronine, type II                             | 14q31.1 | 8.03E-03 | -4.83 | 2.82E-02 | 3.48  |
| 7934297 | -         | Y_RNA ENSG00000201047  | 10q22.1 | 8.36E-03 | 3.82  | 2.14E-02 | 3.17  |
| 8149165 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 8.48E-03 | -3.39 | 9.75E-03 | -3.30 |
| 8149167 | LINC00965 | long intergenic non-protein coding RNA 965                     | 8p23.1  | 8.48E-03 | -3.39 | 9.75E-03 | -3.30 |
| 7918064 | COL11A1   | collagen, type XI, alpha 1                                     | 1p21    | 8.50E-03 | 2.58  | 8.06E-05 | -5.38 |
| 8103520 | TRIM61    | tripartite motif containing 61                                 | 4q32.3  | 8.50E-03 | -2.86 | 7.51E-03 | -2.92 |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |              |  |          |          |       |          |        |
|---------|--------------|--|----------|----------|-------|----------|--------|
| 7986509 | DNM1P46      | dynamin 1 pseudogene 46                                  | 15q26.3  | 8.59E-03 | -4.86 | 3.81E-03 | -6.00  |
| 7986512 | DNM1P46      | dynamin 1 pseudogene 46                                  | 15q26.3  | 8.59E-03 | -4.86 | 3.81E-03 | -6.00  |
| 7986527 | DNM1P46      | dynamin 1 pseudogene 46                                  | 15q26.3  | 8.59E-03 | -4.86 | 3.81E-03 | -6.00  |
| 8105436 | MAP3K1       | mitogen-activated protein kinase kinase kinase 1         | 5q11.2   | 8.62E-03 | 2.07  | 4.76E-07 | 8.08   |
| 8054439 | ST6GAL2      | ST6 beta-galactosamide alpha-2,6-sialyltransferase 2     | 2q11.3   | 8.72E-03 | -2.94 | 6.26E-06 | 11.93  |
| 8124574 | ZSCAN12      | zinc finger and SCAN domain containing 12                | 6p21     | 8.72E-03 | -2.41 | 1.81E-03 | -2.99  |
| 7927186 | RASSF4       | Ras association domain family member 4                   | 10q11.21 | 8.78E-03 | 3.47  | 1.21E-03 | 5.23   |
| 8124654 | GABBR1       | gamma-aminobutyric acid (GABA) B receptor, 1             | 6p21.31  | 8.85E-03 | -2.98 | 1.41E-03 | -4.14  |
| 8164521 | SH3GLB2      | SH3-domain GRB2-like endophilin B2                       | 9q34     | 8.91E-03 | -2.51 | 2.90E-03 | -2.97  |
| 7953981 | ETV6         | ets variant 6  | 12p13    | 8.92E-03 | 2.33  | 7.75E-04 | 3.27   |
| 7945663 | IFITM10      | interferon induced transmembrane protein 10              | 11p15.5  | 8.92E-03 | 3.39  | 2.23E-02 | 2.82   |
| 8148304 | TRIB1        | tribbles pseudokinase 1                                  | 8q24.13  | 9.07E-03 | -2.32 | 1.24E-04 | 4.30   |
| 8040223 | RRM2         | ribonucleotide reductase M2                              | 2p25.1   | 9.41E-03 | 3.26  | 1.33E-03 | 4.74   |
| 8053467 | SFTPB        | surfactant protein B                                     | 2p11.2   | 9.50E-03 | 35.26 | 7.31E-04 | 164.67 |
| 7976816 | SNORD114-3   | small nucleolar RNA, C/D box 114-3                       | 14q32.31 | 9.55E-03 | 6.30  | 7.29E-03 | -6.85  |
| 8179595 | GABBR1       | gamma-aminobutyric acid (GABA) B receptor, 1             | 6p21.31  | 9.67E-03 | -3.36 | 2.08E-03 | -4.57  |
| 8117572 | ZNF391       | zinc finger protein 391                                  | 6p22.1   | 9.84E-03 | -2.51 | 3.64E-03 | -2.92  |
| 7981718 | EPC1         | enhancer of polycomb homolog 1 (Drosophila)              | 10p11    | 1.02E-02 | 10.02 | 2.70E-02 | 6.84   |
| 7919168 | PDE4DIP      | phosphodiesterase 4D interacting protein                 | 1q12     | 1.02E-02 | 2.65  | 1.73E-02 | 2.43   |
| 8143850 | CDK5         | cyclin-dependent kinase 5                                | 7q36     | 1.02E-02 | 2.98  | 2.49E-03 | 3.87   |
| 8155696 | FAM122A      | family with sequence similarity 122A                     | 9q21.11  | 1.04E-02 | -2.25 | 2.48E-04 | -3.78  |
| 8119161 | PIM1         | Pim-1 proto-oncogene, serine/threonine kinase            | 6p21.2   | 1.04E-02 | 2.44  | 1.26E-02 | 2.37   |
| 7981046 | IFI27L2      | interferon, alpha-inducible protein 27-like 2            | 14q32.12 | 1.05E-02 | -2.12 | 2.50E-03 | -2.55  |
| 8178298 | GABBR1       | gamma-aminobutyric acid (GABA) B receptor, 1             | 6p21.31  | 1.05E-02 | -3.24 | 1.63E-03 | -4.69  |
| 8166264 | -            | -  |          | 1.05E-02 | 2.25  | 1.32E-02 | 2.19   |
| 7902913 | CDC7         | cell division cycle 7                                    | 1p22     | 1.06E-02 | 2.97  | 1.95E-03 | 4.05   |
| 8062427 | VSTM2L       | V-set and transmembrane domain containing 2 like         | 20q11.23 | 1.06E-02 | 2.55  | 3.36E-03 | 3.05   |
| 8022803 | GAREM        | GRB2 associated, regulator of MAPK1                      | 18q12.1  | 1.07E-02 | 3.20  | 1.58E-02 | 2.99   |
| 7929282 | HHEX         | hematopoietically expressed homeobox                     | 10q23.33 | 1.07E-02 | -3.39 | 3.08E-02 | 2.71   |
| 8098328 | GALNT7       | polypeptide N-acetylgalactosaminyltransferase 7          | 4q31.1   | 1.08E-02 | -2.02 | 7.96E-06 | 5.16   |
| 8094190 | CC2D2A       | coiled-coil and C2 domain containing 2A                  | 4p15.32  | 1.08E-02 | -2.82 | 3.04E-03 | -3.51  |
| 7996160 | LOC388282    | uncharacterized LOC388282                                | 16q13    | 1.09E-02 | 2.71  | 1.55E-03 | 3.72   |
| 8093171 | MFI2         | MFI2 antisense RNA 1                                     | 3q29     | 1.09E-02 | 3.48  | 9.59E-04 | 5.88   |
| 8157463 | C9orf91      | chromosome 9 open reading frame 91                       | 9q32     | 1.13E-02 | -2.31 | 1.31E-03 | -3.11  |
| 8123951 | ADTRP        | androgen-dependent TFPI-regulating protein               | 6p24.1   | 1.13E-02 | 5.42  | 1.25E-04 | 20.81  |
| 8160033 | SNRPE        | small nuclear ribonucleoprotein polypeptide E            | 1q32     | 1.15E-02 | 2.26  | 1.46E-02 | 2.19   |
| 8022506 | RNU6-702P    | RNA, U6 small nuclear 702, pseudogene                    | -        | 1.17E-02 | 2.26  | 1.40E-02 | 2.21   |
| 8043360 | IGKV3OR2-268 | immunoglobulin kappa variable 3/OR2-268 (non-functional) | 2p11.2   | 1.18E-02 | 2.94  | 9.03E-03 | 3.09   |
| 8158406 | TBC1D13      | TBC1 domain family, member 13                            | 9q34.11  | 1.19E-02 | -2.26 | 3.59E-03 | -2.68  |
| 7986520 | LOC101927628 | uncharacterized LOC101927628                             | 15q26.3  | 1.21E-02 | -4.78 | 6.05E-03 | -5.78  |
| 8104825 | BRX1         | BRX1, biogenesis of ribosomes, homolog (S. cerevisiae)   | 5p13.2   | 1.22E-02 | 2.22  | 1.37E-02 | 2.18   |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |           |   |          |          |       |          |       |
|---------|-----------|---|----------|----------|-------|----------|-------|
| 8053801 | ANKRD36   | ankyrin repeat domain 36                                      | 2q11.2   | 1.25E-02 | -2.38 | 1.06E-02 | -2.46 |
| 7973743 | BNIP3P1   | BCL2/adenovirus E1B 19 kDa interacting protein 3 pseudogene 1 | 14q12    | 1.27E-02 | 2.59  | 3.98E-04 | 4.51  |
| 8081548 | PVRL3     | poliovirus receptor-related 3                                 | 3q13     | 1.29E-02 | -4.93 | 3.52E-02 | -3.69 |
| 7986517 | DNM1P47   | dynamin 1 pseudogene 47                                       | 15q26.3  | 1.31E-02 | -4.80 | 6.20E-03 | -5.91 |
| 7986522 | DNM1P47   | dynamin 1 pseudogene 47                                       | 15q26.3  | 1.31E-02 | -4.80 | 6.20E-03 | -5.91 |
| 8001449 | IRX3      | iroquois homeobox 3   | 16q12.2  | 1.36E-02 | 4.29  | 2.60E-02 | 3.62  |
| 7960177 | SLC6A12   | solute carrier family 6 member 12                             | 12p13.33 | 1.40E-02 | 2.89  | 1.91E-04 | 6.40  |
| 7909127 | MFSD4     | major facilitator superfamily domain containing 4             | 1q32.1   | 1.40E-02 | 2.17  | 2.43E-03 | 2.77  |
| 8150988 | ASPH      | aspartate beta-hydroxylase                                    | 8q12.1   | 1.41E-02 | -2.03 | 4.75E-03 | -2.33 |
| 8159501 | LCN12     | lipocalin 12  | 9q34.3   | 1.41E-02 | -2.76 | 1.43E-02 | 2.75  |
| 8163444 | ZFP37     | ZFP37 zinc finger protein                                     | 9q32     | 1.43E-02 | -3.23 | 1.32E-02 | -3.28 |
| 7943376 | KIAA1377  | KIAA1377  | 11q22.1  | 1.43E-02 | -3.17 | 1.15E-02 | -3.31 |
| 8009417 | KPNA2     | karyopherin alpha 2 (RAG cohort 1, importin alpha 1)          | 17q24.2  | 1.44E-02 | 2.35  | 2.19E-02 | 2.21  |
| 8019737 | KPNA2     | karyopherin alpha 2 (RAG cohort 1, importin alpha 1)          | 17q24.2  | 1.51E-02 | 2.32  | 2.14E-02 | 2.20  |
| 8170630 | PNMA6A    | paraneoplastic Ma antigen family member 6A                    | Xq28     | 1.51E-02 | -2.35 | 5.94E-03 | -2.72 |
| 8172787 | SSX2B     | synovial sarcoma, X breakpoint 2B                             | Xp11.22  | 1.53E-02 | 2.76  | 7.52E-05 | 6.84  |
| 7920264 | S100A5    | S100 calcium binding protein A5                               | 1q21     | 1.56E-02 | 3.10  | 7.21E-04 | 5.85  |
| 8043470 | IGKV3D-11 | immunoglobulin kappa variable 3D-11                           | 2p11.2   | 1.57E-02 | 6.36  | 1.91E-02 | 5.95  |
| 8140840 | STEAP4    | STEAP family member 4   | 7q21.12  | 1.59E-02 | 10.09 | 1.62E-02 | 10.02 |
| 8059852 | MSL3P1    | male-specific lethal 3 homolog (Drosophila) pseudogene 1      | 2q37     | 1.60E-02 | -3.20 | 7.53E-03 | -3.75 |
| 8138527 | STEAP1B   | STEAP family member 1B  | 7p15.3   | 1.65E-02 | 2.32  | 2.87E-03 | 3.01  |
| 8038126 | CA11      | carbonic anhydrase XI   | 19q13.3  | 1.68E-02 | -3.52 | 4.21E-02 | -2.82 |
| 8021169 | LIPG      | lipase, endothelial   | 18q21.1  | 1.69E-02 | -3.83 | 2.51E-04 | 11.09 |
| 8068383 | CLIC6     | chloride intracellular channel 6                              | 21q22.12 | 1.70E-02 | -4.84 | 4.62E-03 | -7.10 |
| 8174937 | TENM1     | teneurin transmembrane protein 1                              | Xq25     | 1.71E-02 | -6.94 | 4.14E-02 | 5.00  |
| 7996027 | CX3CL1    | chemokine (C-X3-C motif) ligand 1                             | 16q13    | 1.72E-02 | 3.54  | 9.46E-03 | 4.07  |
| 8043449 | IGKV3D-20 | immunoglobulin kappa variable 3D-20                           | 2p11.2   | 1.74E-02 | 5.18  | 2.03E-02 | 4.93  |
| 7910398 | RAB4A     | RAB4A, member RAS oncogene family                             | 1q42.13  | 1.75E-02 | 2.40  | 2.11E-02 | 2.33  |
| 8145281 | SLC25A37  | solute carrier family 25 member 37                            | 8p21.2   | 1.76E-02 | 2.59  | 4.30E-03 | 3.32  |
| 7919971 | RFX5      | regulatory factor X, 5 (influences HLA class II expression)   | 1q21.3   | 1.78E-02 | 2.17  | 1.92E-02 | 2.15  |
| 8146839 | C8orf34   | chromosome 8 open reading frame 34                            | 8q13     | 1.79E-02 | 4.29  | 4.52E-03 | -6.40 |
| 8131583 | BZW2      | basic leucine zipper and W2 domains 2                         | 7p21.1   | 1.80E-02 | 2.32  | 2.88E-04 | 4.42  |
| 7940182 | OR4D10    | olfactory receptor, family 4, subfamily D, member 10          | 11q12    | 1.82E-02 | 3.68  | 5.05E-03 | 5.04  |
| 7943803 | DIXDC1    | DIX domain containing 1                                       | 11q23.1  | 1.82E-02 | -2.55 | 1.37E-03 | -4.03 |
| 7960865 | SLC2A3    | solute carrier family 2 member 3                              | 12p13.31 | 1.83E-02 | 4.96  | 7.78E-03 | 6.41  |
| 7986515 | DNM1P47   | dynamin 1 pseudogene 47                                       | 15q26.3  | 1.83E-02 | -4.27 | 1.04E-02 | -4.99 |
| 7986525 | DNM1P47   | dynamin 1 pseudogene 47                                       | 15q26.3  | 1.83E-02 | -4.27 | 1.04E-02 | -4.99 |
| 8133976 | DBF4      | DBF4 zinc finger  | 7q21.3   | 1.90E-02 | 2.23  | 8.51E-03 | 2.52  |
| 8102247 | RPL34-AS1 | RPL34 antisense RNA 1 (head to head)                          | 4q25     | 1.91E-02 | -2.49 | 1.44E-02 | -2.63 |
| 8108301 | KIF20A    | kinesin family member 20A                                     | 5q31     | 1.92E-02 | 3.97  | 1.08E-02 | 4.63  |
| 8131944 | NFE2L3    | nuclear factor, erythroid 2-like 3                            | 7p15.2   | 1.92E-02 | 4.67  | 3.64E-03 | 7.51  |



## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |           |   |          |          |       |          |        |
|---------|-----------|---|----------|----------|-------|----------|--------|
| 7908793 | ELF3      | E74 like ETS transcription factor 3                               | 1q32.1   | 1.93E-02 | 4.56  | 1.40E-04 | 19.55  |
| 8107706 | LMNB1     | lamin B1  | 5q23.2   | 1.93E-02 | 2.02  | 7.06E-04 | 3.17   |
| 8056184 | ITGB6     | integrin, beta 6  | 2q24.2   | 1.95E-02 | 7.26  | 3.44E-05 | 88.60  |
| 8161520 | PGM5      | phosphoglucomutase 5  | 9q13     | 1.99E-02 | -2.07 | 5.79E-08 | -17.86 |
| 7905406 | CGN       | cingulin  | 1q21     | 2.03E-02 | 2.37  | 4.25E-05 | 6.64   |
| 7923189 | KIF14     | kinesin family member 14  | 1q32.1   | 2.04E-02 | 2.55  | 7.59E-03 | 3.05   |
| 7980098 | ALDH6A1   | aldehyde dehydrogenase 6 family, member A1                        | 14q24.3  | 2.04E-02 | -2.36 | 2.34E-03 | -3.38  |
| 8115666 | NUDCD2    | NudC domain containing 2  | 5q34     | 2.06E-02 | 2.21  | 1.65E-02 | 2.28   |
| 8097017 | UGT8      | UDP glycosyltransferase 8   | 4q26     | 2.07E-02 | 3.33  | 4.47E-04 | 7.87   |
| 7981722 | IGHV3-7   | immunoglobulin heavy variable 3-7                                 | 14q32.33 | 2.08E-02 | 9.22  | 4.35E-02 | 6.64   |
| 8040458 | KCNS3     | potassium voltage-gated channel modifier subfamily S member 3     | 2p24.2   | 2.09E-02 | 2.86  | 4.77E-04 | 6.07   |
| 8109612 | ADRA1B    | adrenoceptor alpha 1B   | 5q33.3   | 2.09E-02 | 2.68  | 6.36E-03 | 3.36   |
| 8077899 | PPARG     | peroxisome proliferator-activated receptor gamma                  | 3p25     | 2.11E-02 | 2.86  | 1.13E-02 | 3.25   |
| 8154670 | IFT74     | intraflagellar transport 74                                       | 9p21.2   | 2.12E-02 | -2.55 | 2.49E-02 | -2.47  |
| 8025478 | ZNF559    | zinc finger protein 559   | 19p13.2  | 2.14E-02 | -2.44 | 1.16E-02 | -2.71  |
| 8068833 | PDE9A     | phosphodiesterase 9A  | 21q22.3  | 2.15E-02 | 2.34  | 1.44E-05 | 8.32   |
| 8143663 | EZH2      | enhancer of zeste 2 polycomb repressive complex 2 subunit         | 7q36.1   | 2.23E-02 | 2.77  | 3.40E-03 | 4.04   |
| 7990151 | PKM       | pyruvate kinase, muscle   | 15q22    | 2.25E-02 | 2.26  | 3.91E-02 | 2.06   |
| 8145570 | ESCO2     | establishment of sister chromatid cohesion N-acetyltransferase 2  | 8p21.1   | 2.26E-02 | 3.23  | 7.28E-03 | 4.18   |
| 8161945 | RASEF     | RAS and EF-hand domain containing                                 | 9q21.32  | 2.28E-02 | -2.39 | 1.69E-04 | 5.75   |
| 8021470 | PMAIP1    | phorbol-12-myristate-13-acetate-induced protein 1                 | 18q21.32 | 2.28E-02 | 6.57  | 5.85E-03 | 10.91  |
| 8169235 | FRMPD3    | FERM and PDZ domain containing 3                                  | Xq22     | 2.28E-02 | 3.30  | 1.65E-03 | 6.11   |
| 8167835 | TRO       | trophinin   | Xp11.21  | 2.30E-02 | -2.44 | 1.36E-03 | -3.96  |
| 8110478 | ZNF454    | zinc finger protein 454   | 5q35.3   | 2.33E-02 | -2.56 | 4.51E-03 | -3.44  |
| 8037322 | ETHE1     | ethylmalonic encephalopathy 1                                     | 19q13.31 | 2.37E-02 | 2.37  | 2.19E-02 | 2.40   |
| 8063923 | SLC04A1   | solute carrier organic anion transporter family, member 4A1       | 20q13.33 | 2.38E-02 | 2.35  | 2.25E-03 | 3.47   |
| 7988380 | DUOXA1    | dual oxidase maturation factor 1                                  | 15q21.1  | 2.39E-02 | -2.80 | 3.58E-02 | 2.57   |
| 8147030 | STMN2     | stathmin 2  | 8q21.13  | 2.46E-02 | 4.01  | 9.76E-03 | 5.20   |
| 7910001 | DEGS1     | delta(4)-desaturase, sphingolipid 1                               | 1q42.11  | 2.47E-02 | 2.20  | 5.45E-03 | 2.80   |
| 8083166 | TRPC1     | transient receptor potential cation channel subfamily C member 1  | 3q23     | 2.49E-02 | -2.87 | 3.40E-04 | -7.07  |
| 8126303 | TREM1     | triggering receptor expressed on myeloid cells 1                  | 6p21.1   | 2.53E-02 | 5.91  | 1.73E-03 | 15.39  |
| 8056363 | SLC38A11  | solute carrier family 38, member 11                               | 2q24.3   | 2.55E-02 | 3.06  | 9.82E-03 | 3.80   |
| 8040365 | TRIB2     | tribbles pseudokinase 2   | 2p24.3   | 2.59E-02 | 2.43  | 2.35E-02 | -2.49  |
| 8123936 | NEDD9     | neural precursor cell expressed, developmentally down-regulated 9 | 6p24.2   | 2.60E-02 | 3.74  | 1.21E-02 | 4.60   |
| 8144228 | FLJ36840  | uncharacterized LOC645524   | -        | 2.69E-02 | -2.45 | 2.40E-02 | -2.51  |
| 8044499 | SLC20A1   | solute carrier family 20 (phosphate transporter), member 1        | 2q14.1   | 2.94E-02 | 2.80  | 1.14E-03 | 5.38   |
| 8112376 | CENPK     | centromere protein K  | 5q12.3   | 3.01E-02 | 2.50  | 7.95E-04 | 5.02   |
| 8065719 | PXMP4     | peroxisomal membrane protein 4, 24 kDa                            | 20q11.22 | 3.03E-02 | -5.07 | 1.78E-02 | -6.09  |
| 8084206 | B3GNT5    | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5     | 3q27.1   | 3.08E-02 | 2.63  | 1.52E-02 | 3.05   |
| 8043476 | IGKV1D-43 | immunoglobulin kappa variable 1D-43                               | 2p11.2   | 3.11E-02 | 3.43  | 4.03E-02 | 3.20   |
| 7909601 | SNORA16B  | small nucleolar RNA, H/ACA box 16B                                | 1q32.3   | 3.15E-02 | 2.79  | 1.15E-02 | 3.48   |

## Gene expression and biofunctions related to a brain metastasis from a PTC

|         |             |  |           |          |       |          |        |
|---------|-------------|--|-----------|----------|-------|----------|--------|
| 7940173 | OR5A1       | olfactory receptor, family 5, subfamily A, member 1            | 11q12.1   | 3.25E-02 | 2.36  | 8.99E-03 | 2.96   |
| 7915910 | PDZK1IP1    | PDZK1 interacting protein 1                                    | 1p33      | 3.25E-02 | 8.78  | 7.85E-03 | 16.83  |
| 7953218 | RAD51AP1    | RAD51 associated protein 1                                     | 12p13.32  | 3.26E-02 | 2.07  | 1.71E-03 | 3.26   |
| 8054281 | LONRF2      | LON peptidase N-terminal domain and ring finger 2              | 2q11.2    | 3.32E-02 | -2.47 | 1.89E-02 | 2.77   |
| 8001104 | IGHV3OR16-7 | immunoglobulin heavy variable 3/OR16-7 (pseudogene)            | 16p11.2   | 3.46E-02 | 4.66  | 4.02E-02 | 4.42   |
| 7906930 | NUF2        | NUF2, NDC80 kinetochore complex component                      | 1q23.3    | 3.46E-02 | 2.83  | 1.07E-02 | 3.70   |
| 8124402 | HIST1H1T    | histone cluster 1, H1t   | 6p21.3    | 3.47E-02 | 2.13  | 1.06E-02 | 2.59   |
| 7917503 | GBP3        | guanylate binding protein 3                                    | 1p22.2    | 3.52E-02 | 3.52  | 5.11E-03 | 5.96   |
| 8007071 | CDC6        | cell division cycle 6  | 17q21.3   | 3.52E-02 | 2.21  | 2.13E-03 | 3.59   |
| 8103822 | VEGFC       | vascular endothelial growth factor C                           | 4q34.3    | 3.61E-02 | -2.20 | 7.95E-04 | 4.25   |
| 7990054 | UACA        | uveal autoantigen with coiled-coil domains and ankyrin repeats | 15q23     | 3.66E-02 | -3.02 | 3.65E-02 | -3.02  |
| 8165735 | CSF2RA      | colony stimulating factor 2 receptor alpha subunit             | Xp22.33   | 3.76E-02 | 2.37  | 2.82E-02 | -2.51  |
| 8176306 | CSF2RA      | colony stimulating factor 2 receptor alpha subunit             | Xp22.33   | 3.76E-02 | 2.37  | 2.82E-02 | -2.51  |
| 8096845 | EGF         | epidermal growth factor  | 4q25      | 3.77E-02 | 2.43  | 9.81E-04 | 4.97   |
| 8115397 | FAXDC2      | fatty acid hydroxylase domain containing 2                     | 5q33.2    | 3.80E-02 | -3.10 | 3.54E-03 | -5.63  |
| 7907830 | QSOX1       | quiescin Q6 sulfhydryl oxidase 1                               | 1q24      | 3.85E-02 | 2.56  | 1.37E-02 | 3.19   |
| 7927710 | CDK1        | cyclin-dependent kinase 1                                      | 10q21.1   | 3.89E-02 | 3.32  | 1.03E-02 | 4.75   |
| 8019857 | NDC80       | NDC80 kinetochore complex component                            | 18p11.32  | 3.90E-02 | 2.09  | 5.86E-03 | 2.85   |
| 8169598 | ZCCHC12     | zinc finger, CCHC domain containing 12                         | Xq24      | 3.90E-02 | -3.17 | 5.98E-06 | 35.85  |
| 8146500 | LYN         | LYN proto-oncogene, Src family tyrosine kinase                 | 8q13      | 3.98E-02 | 3.12  | 1.57E-02 | 3.98   |
| 7979505 | SIX1        | SIX homeobox 1   | 14q23.1   | 4.05E-02 | 2.87  | 3.74E-05 | -15.94 |
| 7905731 | UBAP2L      | ubiquitin associated protein 2-like                            | 1q21.3    | 4.11E-02 | 2.13  | 2.60E-02 | 2.30   |
| 7905929 | EFNA1       | ephrin-A1  | 1q21.3q22 | 4.21E-02 | 2.54  | 2.99E-03 | 4.44   |
| 8115623 | ATP10B      | ATPase, class V, type 10B                                      | 5q34      | 4.55E-02 | 2.91  | 3.24E-03 | 5.59   |
| 7932132 | FRMD4A      | FERM domain containing 4A                                      | 10p13     | 4.64E-02 | 2.32  | 4.60E-02 | -2.32  |